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An Assessment of Vaginal Lubrication and Blood Flow

in Women Taking Oral Contraceptive Pills

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An Assessment of Vaginal Lubrication and Blood Flow in Women Taking Oral Contraceptive Pills

by

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Dedication

This dissertation is dedicated to all of the women who participated in this study and to the many individuals who participated in the studies that brought me to this point.

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ABSTRACT

AN ASSESSMENT OF VAGINAL LUBRICATION AND BLOOD FLOW IN WOMEN TAKING ORAL CONTRACEPTIVE PILLS

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The University of Texas at Austin, 2021

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Genital sexual arousal, which consists of genital vasocongestion and lubrication, is critical to healthy sexual function in women and closely linked with hormone function. Oral hormonal contraceptive pills, which are used by over a quarter of reproductive-age women in the United States (Daniels, Daugherty, Jones, & Mosher, 2015; Jones, Mosher, & Daniels, 2013), contain either both ethinylestradiol and a synthetic progestin, or solely a synthetic progestin. Oral hormonal contraceptive pills (OCPs) tend to reduce the number of bioavailable androgens through upregulation of sex hormone binding globulin (SHBG; Zimmerman, Eijkemans, Coelingh Bennink, Blankenstein, & Fauser, 2014), and they have been associated with decrements in self-reported arousal and vaginal lubrication (Hassanin, El-Halwagy, Ismail, & Shehab, 2018; Smith, Jozkowski, & Sanders, 2014). The primary aim of this dissertation was to examine differences in physiological lubrication and vaginal blood flow among women using OCPs with varying androgenic properties, as well as the

possible mediating role of SHBG in these relationships. Participants in this study were 130 women: 59 naturally-cycling control women, 50 women taking androgenic OCPs, and 21 women taking antiandrogenic OCPs. Participants watched sexual films while their sexual arousal responses were measured, completed questionnaires, and took part in a blood draw. Results indicated physiological deficits in women taking either form of OCP, with marked inhibitory effects found in women taking antiandrogenic OCPs. Whereas SHBG did not meaningfully mediate the relationships between study group and physiological sexual arousal response, paths within the models indicated significant relationships among these variables. Rates of sexual dysfunction were significantly greater in the antiandrogenic group compared to control. These results further elucidate the effect of sex steroid hormones on women's sexual arousal response and suggest the presence of physiological sexual side effects of various OCPs. It is recommended that prescribing clinicians consult patients on such physiological effects, and future research should examine the maintenance of these effects after OCP discontinuation.

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CHAPTER 1: INTRODUCTION

1.1. FEMALE SEXUAL AROUSAL

Sexual arousal in women involves both psychological (i.e., subjective) and physiological components that prepare the woman's body and mind for sexual activity (Basson, 2015). Subjective sexual arousal has been conceptualized as the "emotional" (Chivers, Seto, Lalumière, Laan, & Grimbos, 2010; Parish et al., 2016) or "cognitive" (Janssen, Everaerd, Spiering, & Janssen, 2000; Spiering, Everaerd, & Janssen, 2003) state of sexual arousal, and was recently defined as positive mental engagement in response to a sexual stimulus (Althof et al., 2017). Physiological sexual arousal in women involves both genital (e.g., vasocongestion, vaginal lubrication) and nongenital (e.g., increased heart rate, sweating, pupil dilation, hardening and erection of the nipples, and flushing of the skin) responses. The genital arousal component is integral to female sexual response, as genital blood flow and lubrication allow for pain-free penetration in the absence of a genital pain disorder.

The loss or reduction of genital sexual arousal can lead to clinically meaningful distress and can detrimentally affect a woman's sexual function (Leiblum, 2003). Indeed, diminished or absent genital arousal was the defining feature of female sexual arousal disorder in the *Diagnostic and Statistical Manual of Mental Disorders (DSM) III, IV* and *IV-TR* (American Psychiatric Association, 1980, 1994, 2000) and the *International Classification of Disease (ICD) 10* and *11* (World Health Organization, 1992, 2019). In the recently published *ICD-11,* female sexual arousal disorder is described as the absence of or marked reduction in genital responses (lubrication, genital engorgement, and genital

sensitivity), nongenital responses (hardening of the nipples, flushing of the skin, increased heart rate, increased blood pressure, and increased respiration rate), and feelings of sexual arousal (sexual excitement or pleasure). Similarly, the former *DSM-IV* characterized the disorder as the inability to attain or maintain an adequate "lubrication-swelling" response to sexual stimuli. Based largely on these two classification systems, prevalence studies of sexual arousal problems in women have focused primarily on self-reported lack of vaginal lubrication as a defining characteristic of arousal disorder in women. Studies have found that 8-15% of all women and 21-28% of sexually active women report experiencing such difficulties (for a review, see Lewis et al., 2010). Similarly, Bancroft and colleagues (2003) found that 31.2% of heterosexual women in the United States reported lubrication problems over the past month. Within the United Kingdom, the prevalence of persistent lubrication problems, lasting three months or more, ranged from 13% (Mitchell et al., 2013) to 28% (Dunn, Croft, & Hackett, 1999). Similarly, findings from a recent systematic review and meta-analysis indicate a 20.6% prevalence rate of lubrication difficulties among premenopausal women (McCool et al., 2016). It should be noted that prevalence studies often fail to assess the patient's distress regarding the arousal concerns, which is a necessary criterion for assessing clinical relevance. Studies that do assess distress have found that difficulties with lubrication hover around 8% (Burri & Spector, 2011; Shifren, Monz, Russo, Segreti, & Johannes, 2008).

The incidence of lubrication problems is higher among women of peri- or postmenopausal years, with one study reporting that 44% of postmenopausal women experience persistent or recurrent lubrication problems (Rosen, Taylor, Leiblum, &

Bachmann, 1993). When including an assessment of distress associated with lubrication problems, the prevalence drops to about 24% (Bancroft et al., 2003; Shifren et al., 2008). In part to address this increase in genital concerns occurring during menopause, a related but distinct disorder was added to the *DSM-5*, titled genitourinary syndrome of menopause. Genitourinary syndrome of menopause is described as a combination of genital concerns (dryness, burning, and irritation), sexual symptoms (lack of lubrication, discomfort or pain, impaired function), and urinary symptoms (urgency, dysuria, and recurrent urinary tract infections; American Psychiatric Association, 2013). The increase in the prevalence of lubrication and other sexual concerns during menopause is thought to be due to hormonal changes that accompany this transition (for a review, see Bachmann & Leiblum, 2004).

1.2. Genital Sexual Arousal in Women

Genital sexual arousal, an early physiological event in the overall female sexual response, is multifaceted. It is comprised of both central and peripheral components. Central components are aspects of sexual arousal regulated by the central nervous system, such as brain or spinal cord activation in response to sexual stimuli. Peripheral components, on the other hand, are regulated by the peripheral nervous system, which contains both the somatic (i.e., voluntary control of the body) and autonomic (i.e., involuntary control of the body) nervous systems. Peripheral components of genital sexual arousal include but are not limited to, vascular changes such as genital blood flow, smooth muscle relaxation and the production of vaginal lubrication. These systems are assumed to be closely related to hormone function and activity. The focus of this dissertation surrounded two peripheral components of women's genital sexual response: genital blood flow and lubrication.

Within the peripheral nervous system, the autonomic nervous system has been found to play a key role in premenopausal women's sexual arousal (for a review, see Meston, 2000). The autonomic nervous system consists of both the parasympathetic and sympathetic nervous systems. Meston and colleagues reported that moderate activation of the sympathetic nervous system using either exercise (Meston & Gorzalka, 1995, 1996a, 1996b) or ephedrine (Meston & Heiman, 1998) increased genital arousal in premenopausal women. Conversely, suppression of the sympathetic nervous system using clonidine inhibited genital arousal (Meston, Gorzalka, & Wright, 1997). The one study to assess the effects of sympathetic nervous system activation in postmenopausal women found that genital arousal improved in pre- but not in postmenopausal women (Brotto & Gorzalka, 2002). Whereas such activation appears to be highly relevant to genital sexual arousal in premenopausal women, it may be less critical to genital sexual arousal in postmenopausal women. This could be due to hormonal shifts (most notable of which is estrogen loss) that accompany the menopausal transition (Burger, Hale, Robertson, & Dennerstein, 2007). Decreases in estrogen lead to anatomical changes such as a thinning of the vaginal tissue, which reduces the amount of blood that can gather in the genital walls and, hence, the amount of lubrication produced (as reviewed in Tan, Bradshaw, & Carr, 2012).

This dissertation examined changes in vaginal lubrication in a sample of premenopausal women receiving exogenous sex steroid hormones via oral contraceptive pills and compared this novel measure of physiological lubrication against a validated measure of vaginal blood flow. The following sections provide a review of the mechanisms behind these two peripheral components of women's sexual arousal response.

1.2.1. Mechanisms of Genital Blood Flow

The vaginal wall consists of three primary layers: the mucosa, muscularis, and adventitia. The mucosa consists of a stratified squamous (i.e., thin, flat cells) epithelium followed by a layer of connective tissue joining the mucosa and muscularis, referred to as the lamina propria. See Figure 1 for a histology slide depicting a cross-section of the vaginal tissue in a premenopausal woman, which clearly depicts the distinction of the many layers of vaginal tissue.

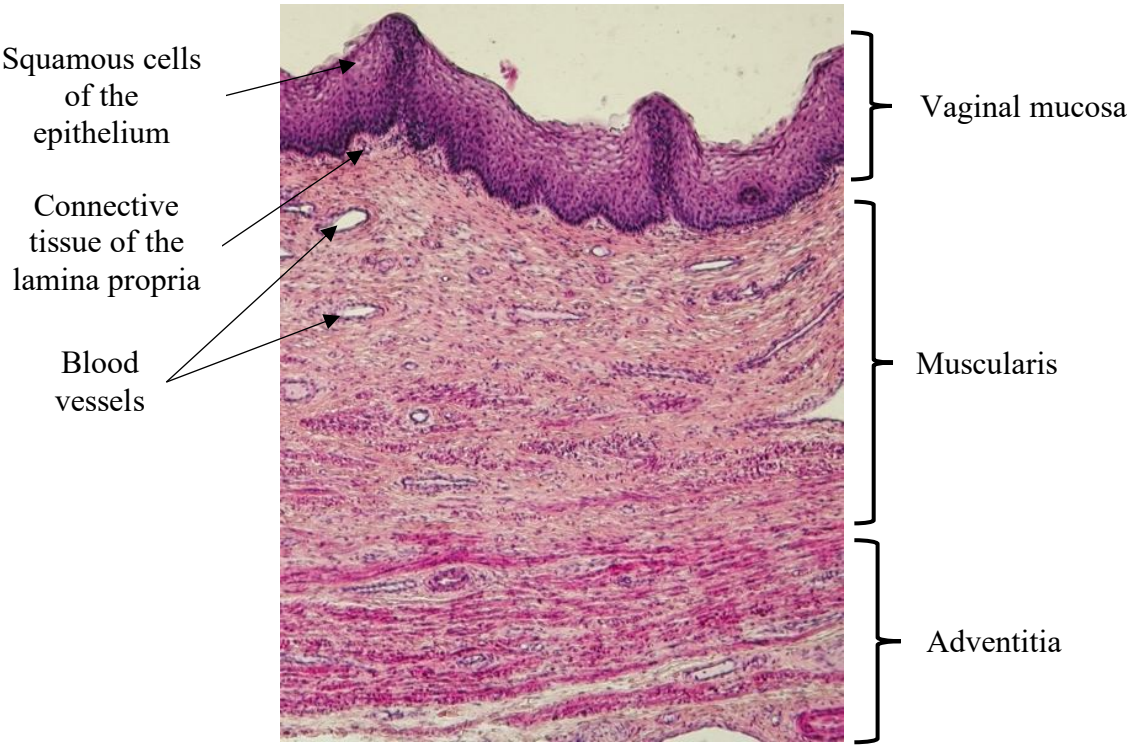

Figure 1. Histology slide indicating the distinct layers of the vaginal tissue in a premenopausal woman. Image courtesy of the Department of Histology, Jagiellonian University Medical College. Permission is granted to copy, distribute and/or modify this document under the terms of the GNU Free Documentation License, Version 1.2 or any later version published by the Free Software Foundation; with no Invariant Sections, no Front-Cover Texts, and no Back-Cover Texts.

As is evident in Figure 1, in premenopausal women, the stratified squamous epithelium folds into numerous ridges throughout the vaginal canal and maintains a moist coating in an unaroused state (for a review, see Jannini, D'Amati, & Lenzi, 2005). During menopause, these ridges flatten and the epithelium thins, decreasing the amount of moisture on the vaginal tissue (Traish, Vignozzi, Simon, Goldstein, & Kim, 2018) and increasing the risk of traumatization of the tissue and subsequent infection (Naumova & Castelo-Branco, 2018). Vaginal tissue has a rich vasculature; the lamina propria contains a dense network of thin-walled blood vessels, as well as elastic fibers and nerve supply, and the muscularis consists of autonomically-innervated smooth muscle and contains numerous blood vessels and arteries. The adventitia, or the outer supportive layer, is rich in collagen and elastin, allowing for the easy expansion and elongation of the vaginal canal during sexual arousal and childbirth.

Autonomic nerve fibers within the vaginal tissue itself produce several peptides; among them, vasoactive intestinal polypeptide and neuropeptide Y have been identified as being particularly relevant to genital blood flow (see Berman, 2005, for a review). Following sexual stimulation, vasoactive intestinal polypeptide and neuropeptide Y are released from nerve endings. Vasoactive intestinal polypeptide then freely interacts with nitric oxide and facilitates smooth muscle relaxation (e.g., Hoyle, Stones, Robson, Whitley, & Burnstock, 1996). This relaxation manifests as an expansion of the diameter of local blood vessels, which reduces resistance and allows for greater vascular inflow. It is generally considered that venous drainage is then reduced, which maintains

vasocongestion and increases the length and diameter of the vaginal canal (Munarriz et al., 2003).

1.2.2. Mechanisms of Vaginal Lubrication

Vaginal lubrication is thought to result from increased genital vasocongestion and occurs both internally (i.e., within the vaginal canal) and externally (e.g., on the labia). Lubrication produced within the vaginal canal is a plasma transudate, which is a thin fluid containing few, if any, cells that have been filtered out of the blood plasma due to an increase in venous pressure (Damjanov, 2009). External lubrication occurs in the form of mucus produced by the Skene's and Bartholin's glands. The Skene's glands are homologous with the male prostate gland, both of which consist of similar structures and histological makeup. The ducts that lead from the Skene's glands are located on the anterior wall of the vulvar vestibule near the urethral opening (Zaviačič, Jakubovská, Belošovič, & Breza, 2000) and secrete a lubricating fluid that contains biochemical markers such as prostate-specific antigen, human urinary protein 1, and phosphodiesterase type 5 (Jannini et al., 2005). The Bartholin's glands are analogous to the bulbourethral (Cowper's) glands in males. The mucus-secreting ducts leading from the Bartholin's glands are located slightly posterior and to the left and right of the vaginal opening (Omole, Simmons, & Hacker, 2003). Lubrication produced by the Skene's and Bartholin's glands slightly moistens the labial opening of the vagina and is thought to be minimal (Masters & Johnson, 1966). Thus, this review focuses on internal lubrication in the form of plasma transudate.

During sexual arousal, blood supply to the vaginal mucosa (i.e., the first layer of the vaginal tissues, which consists of the epithelium and lamina propria) increases,

resulting in increased transudate passing through the vaginal epithelium cells (for a review, see Giraldi & Levin, 2006). In an unaroused state, vaginal fluid has a relatively high potassium and low sodium concentration, with additional, notable concentrations of calcium and chloride (Levin & Wagner, 1977; Stamey & Timothy, 1975; Wagner & Levin, 1978). During sexual arousal, however, the increased transudate passing between cells realizes the cells' capacity for sodium transfer, yielding high concentrations of both sodium and chloride (Levin & Wagner, 1977). In line with the basic principles of osmosis, this fluid cannot be reabsorbed back into the vaginal epithelium cells as the amount of circulating transudate increases and the cells become saturated with sodium. Small droplets of plasma transudate thus move through the epithelium and gather on the vaginal surface, increasing the overall pH of the vaginal canal (e.g., Berman et al., 2001; Wagner, 1979). As the droplets gather, the vagina becomes coated in a moist barrier that protects itself from tearing during penetration (Giraldi & Levin, 2006).

1.3. Measurement of Female Sexual Arousal

As previously described, sexual arousal consists of both subjective and physiological components. Subjective sexual arousal is most often assessed in a laboratory setting immediately before and after the presentation of an erotic film with several Likert-style, self-report questions, though it can also be measured continuously throughout the film (Rellini, McCall, Randall, & Meston, 2005). The Likert-style questions gauge a participant's level of "mental arousal" (or the degree to which she feels "turned on") during the erotic film. Measures of physiological nongenital arousal include both self-report scales and physiological assessment. Typically, self-report scales assess women's perceived

changes in autonomic arousal, such as increases in heart rate, sweating and flushing of the skin (e.g., Heiman & Rowland, 1983), as well as hardening and erection of the nipples. Physiological assessments of nongenital arousal include electrocardiogram (to examine changes in heart rate), galvanic skin response (to measure phasic sweating responses), and eye tracking (to calculate pupil dilation).

Laboratory-based measures of physiological genital arousal include thermistors and thermographic cameras, laser Doppler imaging, ultrasound, magnetic resonance imaging and, most commonly used, photoplethysmography (for a review, see Kukkonen, 2015). As genital blood flow is paramount to physiological genital arousal through its theorized facilitation of both vaginal lubrication and swelling responses, most of these measurement devices provide either direct or indirect assessments of genital vasocongestion.

1.3.1. Labial Thermistor

The labial thermistor is a small disk that attaches to the labia minora. The disk contains a thermometer, which provides a continuous record of changes in surface (i.e., labial skin) temperature (Henson, Rubin, Henson, & Williams, 1977). Although surface temperature is an indirect measure of blood flow, data provided by the labial thermistor do not appear to correlate with more direct measures of blood flow (Prause & Heiman, 2009). Despite this, increases in genital temperature as evidenced by the labial thermistor have been found to be specific to sexual arousal and correlate well with self-report measures of sexual arousal (for a review, see Payne & Binik, 2006). A number of concerns with the labial thermistor have been posited, such as the slow return to baseline that prevents repeated testing, as well as typical fluctuations in body temperature resulting from

environmental and/or menstrual changes that may impact testing (for a review, see Kukkonen, 2015).

1.3.2. Thermographic Cameras

Thermographic cameras remotely record temperature though the assessment of infrared radiation. Radiation emission is directly related to the temperature of the emitting object or body, and the temperature of the object or body can be calculated based on the detected level of radiation (as reviewed in Lahiri, Bagavathiappan, Jayakumar, & Philip, 2012). The remote nature of testing is widely regarded as a benefit of thermographic cameras, as it eliminates the need for the measurement device to come in direct contact with the participant. Similar to the labial thermistor, thermographic cameras serve as an indirect measure of blood flow, and genital temperature has been found to increase specifically to sexual, opposed to neutral, humorous or anxiety-provoking, stimuli (Kukkonen, Binik, Amsel, & Carrier, 2007, 2010). There are also a few limitations to thermographic cameras that should be mentioned. As with the labial thermistor, there is a relatively slow return to baseline period required for repeated testing. A study by Prause and Heiman (2009) suggested that genital temperature requires a 10-minute period to fully return to baseline (i.e., the temperature of an unaroused state). Thermographic cameras also require a consistent ambient temperature and are sensitive to environmental and bodily changes in temperature that may be unrelated to sexual arousal. This could complicate the ability to compare results from different individuals, clinics, or laboratories, as not all testing environments may have the same ambient temperature.

1.3.3. Laser Doppler Imaging

Laser Doppler imaging is the only direct assessment of superficial (i.e., two to three millimeters under the skin) blood flow that does not require genital contact (Waxman & Pukall, 2009). Laser Doppler imaging functions by projecting an infrared laser beam over the skin (Turner, Galarraga, & Khan, 2012). As the light interacts with blood moving under the skin, its speed and direction changes, which is detected and recorded by the device (Wardell, Jakobsson, & Nilsson, 1993). Laser Doppler imaging has been found to discriminate between clinical and non-clinical samples (Boyer, Pukall, & Chamberlain, 2013), and detects changes in blood flow that are specific to sexual, rather than neutral, humorous, or anxiety-provoking, stimuli (Waxman & Pukall, 2009). One notable drawback to the use of laser Doppler imaging is that it takes roughly two to three minutes to complete a single scan (Styles, MacLean, Reid, & Sultana, 2006), therefore continuous measurement throughout a film is not possible.

1.3.4. Ultrasound Probes

The use of ultrasound probes to assess clitoral blood flow has also been examined, though is not generally considered a promising tool for assessing women's sexual arousal in a research context (Kukkonen, 2015). One reason for this is that ultrasound probes must be held in place by a trained sonographer throughout testing, which may be considered invasive and unappealing to potential participants. The need for a trained sonographer also severely limits the ability for this tool to become widespread, as many sexual psychophysiological researchers and clinicians do not have such training. Researchers who have used these probes, however, have found that they are sensitive enough to detect

increases in clitoral blood flow in response to pharmacological agents (Bechara et al., 2003; Caruso et al., 2006). However, the device does not appear to differentiate sexual arousal from control conditions (e.g., humorous stimuli) and has not been found to correlate significantly with subjective sexual arousal (Kukkonen et al., 2006).

1.3.5. Magnetic Resonance Imaging

Few studies have examined the use of magnetic resonance imaging for the assessment of genital sexual arousal in women. Magnetic resonance imaging provides an examination of the genital structure through the use of magnetic fields that develop images of the body (R. W. Brown, Cheng, Haacke, Thompson, & Venkatesan, 2014). Change in clitoral blood volume, opposed to changes in other genital structures such as the labia, appears to be the most reliable index of sexual arousal provided by this method (Maravilla et al., 2005). Indeed, clitoral blood volume has been found to increase during exposure to sexual stimuli (Maravilla et al., 2005; Suh et al., 2004), however, the specificity of this response has yet to be evaluated. The use of magnetic resonance imaging is costly and accessibility is limited, therefore it is unlikely to become a widespread tool to measure sexual arousal (Kukkonen, 2015).

1.3.6. Vaginal Photoplethysmography

The most widely implemented measure of physiological sexual arousal in women is the vaginal photoplethysmograph, which has been used in over 200 published studies to date. The vaginal photoplethysmograph is a clear, acrylic, tampon-shaped device used to detect changes in tissue engorgement. The vaginal photoplethysmograph was designed to be easily inserted by the participant, and a positioning shield can be placed on the device's

cord in order to standardize the location and depth of insertion between uses (Laan, Everaerd, & Evers, 1995). The vaginal photoplethysmograph contains a light-emitting diode or transistor that emits either infrared or incandescent light. After emission, the light reflects off of blood that has gathered in the capillary bed of the vaginal canal and is subsequently detected by the device (Hoon, Wincze, & Hoon, 1976; Sintchak & Geer, 1975). The quantity of light that is detected by the device directly relates to the transparency of the vaginal tissue, where less transparency (i.e., more blood in the genital walls) facilitates greater amounts of back-scattered light. Therefore, the device serves as an indirect measure of vasocongestion. Vaginal pulse amplitude (VPA), the corresponding unit of physiological sexual arousal provided by the device, is believed to reflect phasic changes in vaginal engorgement with each heartbeat, such that greater pulse amplitudes indicate greater engorgement (e.g., Geer, Morokoff, & Greenwood, 1974). Vaginal photoplethysmography is both a sensitive and reliable index of women's physiological sexual arousal (Laan et al., 1995). Vaginal pulse amplitude has consistently been found to increase specifically during exposure to erotic stimuli rather than anxiety-provoking stimuli, which also produce physiological activation (e.g., Hamilton & Meston, 2011; Laan et al., 1995; Prause & Heiman, 2009). This suggests that VPA is uniquely sensitive to sexual, as opposed to bodily, arousal.

1.3.7. Vaginal Lubrication

There is currently no common objective measurement of women's lubrication response implemented by researchers (Graham, 2010). Although objective measures (e.g., cotton swabs) have been used in animal models, their application to humans has been

limited. Early studies of vaginal lubrication primarily examined the quantity of lubrication during unaroused states using cotton swabs (Stone & Gamble, 1959), tampons (e.g., Godley, 1985; Odeblad, 1964; Preti, Huggins, & Silverberg, 1979), and evaporimeters (Wagner, 1979). Cotton swabs and tampons function as methods of collecting vaginal lubrication, whereas evaporimeters measure humidity within the vagina. Cotton swabs and tampons are historically the most commonly used methods of assessing vaginal lubrication, though their use in humans has not been reported in the scientific literature for at least three decades. Tampons and cotton swabs are weighed on a calibrated scale before and after being worn in the vaginal canal and may be worn for varying lengths of time, such as six (Preti et al., 1979) to eight hours (Godley, 1985). Using tampons, Preti and colleagues (1979) and Riley and Riley (1983) observed substantial increases in lubrication within the vaginal canal following sexual stimulation and orgasm, respectively. However, due to the high absorbency and wicking capacity of tampons and cotton swabs, repeated testing is not recommended as the vaginal epithelium may become atypically dry (Levin, 2003). Significant increases in vaginal moisture following sexual stimulation have also been detected by an evaporimeter, which is a device that measures the humidity of the vaginal canal (Wagner, 1979).

Recently, the use of litmus strips has been assessed in the measurement of vaginal lubrication (Carranza-Lira et al., 2003; Dawson, Sawatsky, & Lalumière, 2015). Carranza-Lira and colleagues (2003) measured changes in basal vaginal lubrication (i.e., lubrication during an unaroused state) in 40 postmenopausal women before and three months after initiating a regimen of estrogen-based hormone replacement therapy. The litmus strips,

which were placed at the base of the vaginal introitus (i.e., vaginal opening), detected significant increases in lubrication from pre- to post-treatment, suggesting that the estrogen-based treatment was effective at increasing vaginal lubrication. Using litmus strips and the protocol outlined by Carranza-Lira and colleagues (2003), Dawson and colleagues (2015) later examined changes in lubrication in response to sexual and nonsexual stimuli in a small sample ($N = 19$) of sexually healthy, premenopausal women. Significantly greater levels of lubrication were found following the sexual films in comparison to the nonsexual films, suggesting that the litmus strips are sensitive enough to detect lubrication produced in response to sexual arousal.

Studies using litmus strips to measure vaginal lubrication have a few limitations. One drawback to their use, for example, is that they are not commonly ruled. Rather, the length of discoloration (which indicates moisture absorbed by the paper) must be measured with calipers. This requires the use of additional equipment and may have the potential to introduce measurement error. Additionally, as litmus strips were not designed for the assessment of moisture production but rather the pH of a liquid, the wicking capacity will vary based on the composition of the strip; rates of water absorption vary within and between plastics and paper (e.g., Gáspár, Benko, Dogossy, Réczey, & Czigány, 2005; GE Healthcare, 2020). This could lead to inconsistent measurements across clinics and laboratories.

In an effort to circumvent these issues, Handy and Meston (2018a) introduced the use of the Schirmer Tear Test strips for measuring vaginal lubrication. These strips are approved by the Food and Drug Administration for the clinical assessment of dry eyes, and

are also commonly used in clinical research examining moisture produced by mucous membranes such as the eyes (e.g., Sall, Stevenson, Mundorf, & Reis, 2000), nose (e.g., Lindemann et al., 2014) and mouth (e.g., López-Jornet, Camacho-Alonso, & Bermejo-Fenoll, 2006). These test strips are ruled in millimeters, which alleviates the need for calipers or other measurement devices and may facilitate more accurate interrater reliability. They were designed with the intention of measuring moisture production and are made from Grade 41 quantitative filter paper, which is a type of ashless filter paper that facilitates fast and consistent wicking throughout the test strip.

Handy and Meston (2018a) assessed the utility of the Schirmer Tear Test strips for measuring vaginal lubrication in a sample of 64 women with (n = 32) and without (n = 32) sexual arousal concerns. In that study, both groups of women exhibited significant increases in physiological vaginal lubrication in response to a sexual film. However, no between-group differences were observed for pre- nor post-film levels of lubrication. Moderate correlations were found between physiological lubrication and perceived genital arousal (r = .41) and lubrication (r = .30); similar correlations between physiological lubrication and perceived genital arousal were reported by Dawson et al. (.51; 2015) and Sawatsky et al. (.37; 2018) with litmus test strips. Use of the Schirmer Tear Test strips appears to be a viable option for assessing physiological lubrication in women. As the Handy and Meston (2018a) study was preliminary in nature, more research is needed to determine the psychometric properties of this application.

1.4. Hormonal Modulation of Genital Sexual Arousal

Sex steroid hormones are critical to women's sexual function, and large quantities of androgen, estrogen, and progesterone receptors are present in vaginal tissue (Hodgins, Spike, Mackie, & MacLean, 1998). The term 'androgen' refers to a variety of sex steroid hormones including dehydroepiandrosterone, androstenedione, testosterone, and 5α-dihydrotestosterone (Bolour & Braunstein, 2005). To properly reflect the terminology used in the scientific literature (e.g., Davis, Worsley, Miller, Parish, & Santoro, 2016), the term 'androgen' is used in this dissertation as a generic reference to any of its forms (e.g., testosterone) or precursors (e.g., dehydroepiandrosterone).

Androgens have been shown to facilitate both sexual desire and physiological sexual arousal (see Davis et al., 2016, for a review) whereas estrogens facilitate arousal and appear to have little to no effect on desire (see Santoro, Worsley, Miller, Parish, & Davis, 2016, for a review). Estrogens are potent sex steroid hormones that are critical to female fertility, reproductive health, and sexual health. Estradiol, a secreted hormone, modulates the structure and function of genital tissues (as reviewed in Hobeika, Armouti, Kala, & Stocco, 2020). Specifically, estrogens have vasodilatory and vasoprotective effects that regulate blood flow into and out of the vagina and clitoris. Reductions in estradiol have been associated with reduced vaginal blood flow, which likely results in reduced vaginal lubrication (Nappi & Polatti, 2009). Progestins are thought to moderate the forceful effects of estrogens on vaginal tissue (Rosenfield, Cooke, & Radovick, 2014) and may inhibit smooth muscle cell growth (Kayisli et al., 2015) and, in turn, vasodilation and lubrication. As precursors to the biosynthesis of estrogens, androgens are also important for the vitality

of vaginal tissues and are necessary for vaginal function (Cohen & Goldstein, 2016). The following sections review key hormonal pathways in women's genital sexual arousal response.

1.4.1. Sex Steroid Hormones and Genital Blood Flow

Sex steroid hormones influence genital vasocongestion through two primary mechanisms: by 1) maintaining the structural and vascular integrity of the vaginal tissue, and 2) regulating the expression of neurotransmitters and proteins that facilitate blood flow.

1.4.1.1. Hormones and the Structural Integrity of the Vaginal Tissue

Estrogens and androgens play important roles in maintaining the physiological integrity of many tissues, including vaginal tissue (S. R. Davis & Tran, 2001; McEwen, 1999). They do so by regulating distinct cellular processes within the tissue of the vagina, such as the growth and function of neurons, blood vessels, smooth muscle, and cells within the endothelium and epithelium (for reviews, see Davis et al., 2016; Santoro et al., 2016). This keeps capillary beds lush and vaginal tissue healthy. This relationship is clearly evidenced in women transitioning through menopause; decreases in estrogen levels often lead to a thinning of the vaginal tissue (for a review, see Bachmann & Leiblum, 2004) and difficulties with sexual function (Dennerstein, Randolph, Taffe, Dudley, & Burger, 2002).

Researchers have suggested that estrogen is particularly important for the maintenance of the vaginal mucosal epithelium (I. Goldstein, Traish, & Kim, 2004). For example, one study examined the potential differential effects of various sex steroid hormones on tissue structure within the rat vagina (Pessina, Hoyt, Goldstein, & Traish, 2006). In this study, rats were ovariectomized to isolate hormonal effects and were

provided with varying quantities and combinations of estradiol, progesterone, and testosterone over the course of two weeks. Estradiol increased the thickness of the vaginal epithelium to a thickness that was *greater* than that of non-ovariectomized rats, whereas the administration of either progesterone or testosterone did not influence epithelial growth. However, the authors stated that the co-administration of estradiol plus progesterone or testosterone yielded tissue *most similar* to that of non-ovariectomized rats. That is, whereas the treatment of estradiol alone produced atypical thickening of the epithelium, the co-administration of estrogen and progesterone or testosterone facilitated typical, or comparatively less, epithelium growth. When examining the muscularis, which is the middle layer of the vaginal wall made up of smooth muscle, improvements were only seen in rats that received estradiol alone. In fact, the co-administration of estradiol and progesterone or testosterone buffered these effects, yielding thinner tissue than that seen in the estradiol-alone group. This suggests that estradiol is critical to vaginal tissue structure, and testosterone and progesterone may moderate these effects. This improvement in tissue structure likely mediates improvements in genital blood flow, as fuller tissue allows for a greater density of capillary beds and increased blood supply to the genitals (see Mac Bride, Rhodes, & Shuster, 2010, for a review).

Research has also suggested that androgens may be relevant to the maintenance of the vaginal epithelium. In one study examining this topic, twenty-one postmenopausal women with breast cancer were treated with intravaginal testosterone in doses of either 150 or 300 micrograms (μg) daily for 28 days, at which point a vaginal maturation index assessment was performed (Witherby et al., 2011). The vaginal maturation index is the

ratio of parabasal (i.e., immature cells that are not affected by estrogen and progesterone) to superficial (i.e., mature cells that have been affected by estrogen) cells in the vaginal epithelium, where greater vaginal maturation index scores indicate greater amounts of estrogen stimulation (for a review, see McEndree, 1999). In the group of women receiving the 300 μg dose, the vaginal maturation index increased from 20 to 40%, indicating that topical testosterone facilitated the beneficial effects of estrogen on the vaginal epithelium. Women also reported significant decreases in vaginal dryness over the course of the study. This suggests that bioavailable androgens aide estrogen in stimulating (i.e., interacting with) vaginal tissue. Therefore, the presence of both estrogens and androgens appears to benefit vaginal tissue structure.

1.4.1.2. Functional Modulation of Vasocongestion

Sex steroid hormones also modulate vascular components of vaginal tissue by regulating the activities of neurotransmitters and proteins such as vasoactive intestinal polypeptide and nitric oxide. Vaginal tissue has a dense supply of vasoactive intestinal polypeptide and nitric oxide immunoreactive fibers (Hoyle et al., 1996), and their activities appear to be largely hormone-dependent. For example, research has shown that vasoactive intestinal polypeptide fails to increase vaginal blood flow in estrogen-deprived women (Palle, Bredkjœr, Fahrenkrug, & Ottesen, 1991). Palle et al. (1991) provided exogenous vasoactive intestinal polypeptide to six postmenopausal women receiving hormone replacement therapy and six postmenopausal women who were not receiving hormone replacement therapy and measured changes in vaginal blood flow. Significant increases in vaginal blood flow were evidenced only in women receiving hormone replacement

therapy, suggesting that the sex steroid hormones estrogen and progestin influence vasoactive intestinal polypeptide function. This, in turn, appears to facilitate vasocongestion. Similarly, animal models indicate that estrogen is critical for nitric oxide-dependent smooth muscle relaxation (H. W. Kim, Kim, Seo, & Lee, 2002), vaginal blood flow (S. W. Kim et al., 2004) and lubrication (Min et al., 2003). In a study conducted by Berman, McCarthy, and Kyprianou (1998), estrogen replacement therapy resulted in significant increases in nitric oxide expression in ovariectomized compared to intact animals. The authors posited that estrogen may be necessary for the regulation of vaginal nitric oxide expression and that nitric oxide expression may modulate vaginal blood supply and relaxation of smooth muscles (c.f. Al-Hijji, Larsson, & Batra, 2000).

In addition to estrogens, androgens are important to genital blood flow in women. Not only have androgen receptors been found throughout the vaginal tissue (Baldassarre et al., 2013), but androgens are also precursors in estrogen biosynthesis (Simpson, 2003). In other words, estrogens are formed through the aromatization of various androgens. Androgens also have vasodilatory effects (Aversa, Isidori, Spera, Lenzi, & Fabbri, 2003), which enhance blood flow and likely subsequent lubrication. The precise role of androgens on vaginal blood flow and tissue structure is currently unknown (Berman et al., 2003), but researchers have theorized that androgens and estrogens may interact to facilitate sexual arousal. To examine this, Min and colleagues (2002) treated ovariectomized animals with either estradiol or testosterone and measured changes in genital blood flow. Compared to non-ovariectomized animals, significant increases in genital blood flow were found only in those treated with estradiol; treatment of testosterone did not restore genital blood flow.

Unfortunately, combination treatments were not examined in this study, though these results corroborate findings presented in Pessina et al. (2006) and Witherby et al. (2011). Thus, it is likely that interactions between androgens and estrogens are most beneficial to maintaining healthy vaginal tissue and blood flow in women.

1.4.2. Sex Steroid Hormones and Vaginal Lubrication

The effect of hormones on vaginal lubrication is largely thought to be secondary to the effects of hormones on the vaginal structure and vascular functions. As reviewed above, animal models indicate that estrogens and androgens modulate genital blood flow and therefore the production of lubrication (e.g., Min et al., 2002). Some direct effects of sex steroid hormones on lubrication have been noted in the literature (for a review, see Burrows, Basha, & Goldstein, 2012), though their exact acting mechanisms are unknown. For example, androgens have been found to play a necessary role in the glycoprotein synthesis required for vaginal mucification (Kennedy & Armstrong, 1976), which is characterized by changes in the cells of the epithelium from squamous (i.e., flat) to columnar (i.e., tall), mucus-secreting cells (for a review, see Westwood, 2008). Thus, a relative androgen deficiency, which could be manifest in low levels of bioavailable androgens, may contribute to vulvar and vaginal dryness.

In addition to androgens, estrogens appear to be beneficial for vaginal lubrication. In a prospective, randomized control trial examining the effects of ethinylestradiol on sexual function in postmenopausal women, Sarrel (1990) reported that those treated with ethinylestradiol reported improvements in vaginal blood flow and dyspareunia, which refers to difficulty or pain associated with vaginal penetration (Heim, 2001). However,

when these women were treated with the progestin medroxyprogesterone, decreases in vaginal blood flow and increases in dyspareunia were found. Similar beneficial effects of estrogens in combination with androgens on dyspareunia and vaginal lubrication have been reported by others (Sherwin & Gelfand, 1987). Estrogens and androgens may therefore positively impact vaginal dryness and dyspareunia, and progestins may blunt these beneficial effects (Sarrel, 1990, 2002).

1.5. Oral Contraceptive Pills

The use of animal models in research has facilitated a substantial body of literature elucidating the influence of hormones on sexual arousal. Studying women who are currently using hormonal contraceptives offers an alternative and complementary means to animal models for exploring this topic. Oral contraceptive pills (OCPs) are the most common form of hormonal contraception, with a prevalence rate of 28% among reproductive-age women in the United States (Daniels et al., 2015; Jones et al., 2013). Variations in women's sexual arousal response by the hormonal composition of OCPs were the primary focus of this dissertation.

1.5.1. Conception and Contraception

Pregnancy occurs when a sperm fertilizes an egg, which then successfully implants in the uterine lining. Prior to ovulation, estrogen levels peak, which causes the pituitary gland to release a surge of follicle stimulating hormone and luteinizing hormone (for a review, see Watson & Stacy, 2011). The rise in follicle stimulating hormone facilitates the maturing of eggs within the ovaries (as reviewed in Hillier, 1994). Once mature, a single egg from one ovary is released, and the body reabsorbs the remaining matured eggs. The

release of luteinizing hormone triggers the thickening of the uterine lining in preparation for the implantation of a fertilized egg (Watson & Stacy, 2011).

The mature egg travels from the ovary through the fallopian tubes, where a sperm may fuse with and fertilize the egg. After fusion, the cells within the egg begin dividing and the egg continues traveling through the fallopian tubes towards the uterus, where it embeds within the uterine lining (see Marieb & Hoehn, 2016, for a review). The follicle that released the egg transforms into a corpus luteum, which is a cluster of sex steroid hormone-producing cells. The corpus luteum induces is a large surge in progesterone and a small increase in estrogen, which assists in the production of the uterine lining and protects against shedding (i.e., menstruation; Watson & Stacy, 2011). Specifically, the surge in progesterone initiates the transformation of the uterine lining from proliferative to secretory, reflecting increased thickness of the lining in preparation for egg implantation. If no egg implants within the walls, progesterone levels fall, the endometrium breaks down, and the menstrual cycle resumes (see Hobeika et al., 2020, for a discussion).

Whereas non-hormonal forms of contraception work by preventing sperm from reaching the egg (e.g., condoms) or by blocking the reproductive function (i.e., surgical sterilization), hormonal methods (e.g., some intrauterine devices, OCPs) operate by either preventing an egg from being released or preventing a fertilized egg from implanting in the uterus. Oral contraceptive pills contain synthetic hormones. There are two main classes of OCPs: combined OCPs, which contain synthetic estrogen and progestin, and progestin-only pills. The exogenous hormones provided by both combined OCPs and progestin-only pills are metabolized in the liver and, in response to this, the liver increases the production

of the protein sex hormone binding globulin (SHBG; for a review, see Stuckey, 2008). As the name suggests, sex hormones bind to SHBG and are rendered inactive. Of estrogens, progesterone, and androgens, androgens have the highest affinity for SHBG and are thus most likely to bind to this globulin and become inactive (Rosner, 1991). Certain progestins (e.g., doestrogel) increase liver production of SHBG to a greater extent than others (e.g., levonorgestrel); the production of SHBG will increase or decrease based on the androgenic or antiandrogenic properties of the progestin (see Darney, 1995, for a review). The decrease in ovarian production of sex hormones and increase in production of SHBG can result in roughly a two-thirds reduction of bioavailable androgens (for a review, see Zimmerman, Eijkemans, Coelingh Bennink, Blankenstein, & Fauser, 2014).

Oral contraceptive pills inhibit the production of follicle stimulating hormone and luteinizing hormone within the pituitary gland (Rivera, Yacobson, & Grimes, 1999). Without the rise in follicle stimulating hormone levels, follicles do not facilitate the maturing and release of eggs from the ovaries, and ovulation is therefore suppressed (Frye, 2006). The consistently low levels of luteinizing hormone maintain a thin uterine lining that is inhospitable to the implantation of an egg if ovulation were to occur. It is for this reason that OCPs are often prescribed for the management of menorrhagia, or heavy menstrual bleeding (Farquhar & Brown, 2009): a thinner uterine lining will lead to lighter menstrual bleeding.

The inhibition of follicle stimulating hormone and luteinizing hormone also significantly reduces the ovarian production of the sex steroid hormones estrogen, progesterone, and androgens. As the ovaries are the primary production source of these

hormones in women (Hobeika et al., 2020), the bodies of women taking OCPs rely on the synthetic hormones within the pill. Many OCPs provide the body with hormones similar in concentration to that of a post-ovulatory state (i.e., high doses of progesterone coupled with low doses of estrogen; see Rivera et al., 1999), which further protects against pregnancy by leading the body to believe that ovulation recently occurred, and an egg should therefore not be released.

1.5.2. Combined Oral Contraceptive Pills

Combined oral contraceptive pills contain synthetic forms of the hormones estrogen and progestin. Almost all combined OCPs contain ethinylestradiol, a synthetic estrogen. The concentration of ethinylestradiol varies by brand (typically between 15-50 μg) but is most often around 35 μg per pill (van der Westhuizen & van der Merwe, 2011). The primary way in which combined OCPs differ from one another is through their progestin component. Typical combined OCPs contain progestins from four main families: derivatives of 19-nortestosterone (estranes and gonanes), derivatives of 17α-hydroxyprogesterone (pregnanes), derivatives of 19-norprogesterone (norpregnanes), and one derivative of spironolactone (Schindler et al., 2003). As combined OCPs all suppress the production of estrogen, luteinizing hormone and follicle stimulating hormone (Rivera et al., 1999), they are all considered anti-estrogenic and anti-gonadotropic. The extent to which they are antiandrogenic varies by family: derivatives of 19-nortestosterone tend to lack androgenic effects, derivatives of 19-norprogesterone have varying degrees of androgenic activity, and 17α-hydroxyprogesterone derivatives and drospirenone, the sole

derivative of spironolactone, may exert antiandrogenic (i.e., antagonistic) activity (Schindler et al., 2003).

1.5.3. Progestin-Only Pills

Progestin-only pills contain a progestin without estrogen. For that reason, progestin-only pills are particularly suited for women where the estrogen in combined OCPs is contraindicated (e.g., women over 35 who smoke cigarettes), for breastfeeding mothers, and for older women. Similar to combined OCPs, progestin-only pills also suppress the production of estrogen, luteinizing hormone and follicle stimulating hormone (Rivera et al., 1999), and are therefore also considered anti-estrogenic and anti-gonadotropic. Common progestin-only pills contain low doses of 19-nortestosterone derivatives gonanes (e.g., levonorgestrel and desogestrel) or estranes (e.g., norethindrone or ethynodiol diacetate). To minimize adverse androgenic effects (e.g., oily skin, weight gain), the progestin dose in progestin-only pills is typically lower than that found in combined OCPs (de Melo, 2010).

1.6. Oral Contraceptive Pills and Sexual Function

Given the importance of estrogens and androgens and potential inhibitory role of certain progestins in genital blood flow and subsequent lubrication, it is possible that combined OCPs containing antiandrogenic progestins (e.g., 17α-hydroxyprogesterone derivatives, drospirenone) may negatively impact female sexual arousal. The following sections review the current research on the relationship between OCPs and sexual function.

1.6.1. Combined Oral Contraceptive Pills and Sexual Function

Research examining the effects of combined OCP use on sexual function is mixed. Whereas some studies report improvements in sexual function (Çetin, Keskin, Verit, & Yücel, 2015), a recent review of the literature indicated that decreases in lubrication, increases in vestibular pain, and thinning of the labia minora and vaginal introitus are common among combined OCP users (Burrows et al., 2012). Indeed, an internet-based cross-sectional study examining combined OCP use and women's sexual function found that women taking combined OCPs reported greater levels of vaginal dryness and sexual pain as well as decreased lubrication, arousal, pleasure, and orgasm frequency compared to women using nonhormonal forms of contraception (Smith et al., 2014). The authors suggest that these findings may be related to decreases in bioavailable androgens and direct structural effects of combined OCPs on the vagina. Indeed, the type (Pazandeh et al., 2017) and dose (Strufaldi et al., 2010) of estrogen have been implicated in sexual health outcomes. In an extensive study involving 2,612 healthy medical students, similar findings were noted. Women taking combined OCPs scored significantly lower on the Female Sexual Function Index (FSFI; Rosen et al., 2000), the gold standard self-report measure of female sexual function, than did women using other forms of contraception (Wallwiener et al., 2015). However, the authors did not find any effect of estrogen dose or progestin type on self-reported sexual function, which suggests that changes in the number of bioavailable androgens may not have as large of an effect on sexual function as others have suggested (as reviewed in Bachmann et al., 2002). However, Wallwiener and colleagues (2015) proffered that any effects of estrogen dose or progestin type on sexual function may

have been masked by confounding variables such as frequency of sexual activity. That is, if women had not recently (i.e., within the past four weeks, as is required for the FSFI) engaged in penetrative vaginal intercourse, their FSFI scores would have been lower than those of their counterparts. As this was not controlled for in the Wallwiener et al. study, effects of the OCP on FSFI scores could have been overshadowed by the effect of sexual inactivity on FSFI scores.

One limitation of the literature on combined OCP use and sexual function is the lack of randomized clinical trials. One recent study that attempted to address this limitation examined changes in self-reported sexual function in 340 healthy women who were randomized to a common combined OCP (150 μg levonorgestrel and 30 μg ethinylestradiol) or placebo for 3 months (Zethraeus et al., 2016). Sexual function was measured via the Profile of Female Sexual Function (McHorney et al., 2004), a self-report scale assessing various domains of sexual function, at pre- and post-treatment. No differences emerged on overall sexual function; however, women in the combined OCP group scored significantly lower on the desire, arousal and pleasure domains compared to placebo at post-treatment. The authors speculated that there may be a "direct negative effect of the progestin component" of combined OCPs on sexual function (pp. 4050).

1.6.2. Progestin-Only Pills and Sexual Function

The effect of progestin-only pills on sexual function has received considerably less empirical attention than that of combined OCPs. However, a recent study examined self-reported sexual function (via the FSFI) among roughly 100 women using various forms of hormonal contraception (i.e., intrauterine devices, progestin injections, combined OCPs,

and progestin-only pills) against 100 women who were not using hormonal contraception (Hassanin et al., 2018). Results indicated that FSFI desire, arousal, lubrication, and overall sexual function scores were significantly lower among contraceptive users compared to controls, and these results were maintained when comparing women taking any OCP (i.e., combined OCPs or the progestin-only pill) against controls. When the authors parsed apart the type of OCP women were using, they found that the FSFI desire, arousal, lubrication, orgasm, and overall sexual function scores were significantly lower in the progestin-only pill group compared to controls. Similarly, these domains were significantly lower in the progestin injection group compared to controls. The authors suggested that temporary contraceptive use can negatively affect sexual function, and this may be particularly true for progestin-based contraceptives. Similar reports have been described elsewhere in the literature (e.g., Pazandeh et al., 2017).

1.7. Oral Contraceptive Pills may Alter Physiological Sexual Arousal

Only one study to date has prospectively examined the effect of OCP use on physiological sexual arousal. In this laboratory-based study, sexual arousal was measured in a relatively small sample ($N = 16$) of premenopausal women who were about to begin a self-selected regimen of OCP use (Seal, Brotto, & Gorzalka, 2005). Women watched a short neutral-erotic film sequence while their physiological sexual arousal was measured continuously through the use of a vaginal photoplethysmograph both before and six weeks after beginning OCP use. To determine whether there was an effect of the OCP on physiological sexual arousal (i.e., vaginal blood flow), Seal and colleagues compared the change in vaginal pulse amplitude (VPA) throughout the neutral-erotic film sequence

during the pre-treatment session against that of the post-treatment session. Results indicated a significant increase in VPA throughout the neutral-erotic film sequence at pre-treatment only. After six weeks of OCP use, there was no significant increase in VPA when all women's data were analyzed together. However, when examining women's responses at the individual level, the authors reported tremendous variability at post-treatment; some women showed *larger* increases in VPA throughout the film sequence than they had pre-treatment, whereas some women showed smaller increases or even some *decreases* in VPA compared to their individual pre-treatment responses. These differences were only evident when examining each woman's responses individually; examining all post-treatment responses together masked this variability and yielded no significant increase in VPA.

It is important to note that participants in this study were taking a variety of OCPs; the form of OCP (i.e., combined OCP or progestin-only pill), dose of ethinylestradiol, and type and dose of progestin (e.g., norethindrone, levonorgestrel) provided by the pill was not regulated. The authors suggested that the variability seen in women's VPA responses at post-treatment might reflect the varying hormonal compositions of the OCPs. Therefore, a more comprehensive examination of the potential effects of the estrogen and progestin component of OCPs on sexual function is warranted.

1.7.1. Potential Estrogen-Based Effects

Estrogens and progestins increase SHBG production, which results in decreased bioavailable androgens due to their binding affinity for SHBG. In other words, the more SHBG, the fewer bioavailable androgens. Oral contraceptive pills that contain low doses of estrogens, or estrogens plus androgenic progestins, have been found to have less of an

effect on SHBG than those with high doses of estrogens (Zimmerman et al., 2014). This minimized production of SHBG allows for a greater number of bioavailable androgens, which may then lead to greater vaginal blood flow and subsequent lubrication through the stimulation of androgen receptors. It is, therefore, possible that better physiological sexual arousal would be observed in women taking OCPs containing low, rather than high, doses of estrogens.

While this has yet to be studied directly, researchers have examined the relationship between combined OCP use and quantity of bioavailable androgens in women with hypoactive sexual desire disorder (Warnock, Clayton, Croft, Segraves, & Biggs, 2006). In this study, it was found that women who were taking combined OCPs had significantly lower counts of bioavailable androgens than did those who were not taking combined OCPs. The authors suggested that women taking combined OCPs may have developed hypoactive sexual desire disorder as a drug-induced adverse effect due to the low levels of bioavailable androgens, as the facilitatory role of androgens in sexual desire is well-established (Pfaus, 2009). A similar mechanism for adverse physiological sexual side effects may also be possible.

1.7.2. Potential Progestin-Based Effects

The progestin component of OCPs may also affect sexual arousal. Progestins with minimally androgenic or antiandrogenic effects likely increase SHBG. As androgens have a high binding affinity for SHBG (Rosner, 1991), greater quantities of SHBG would allow for a greater number of androgens to bind and become inactive. This would decrease the number of bioavailable androgens. Androgenic progestins, on the other hand, may decrease

the estrogen-induced production of SHBG (as reviewed in Sitruk-Ware, 2004). Such a decrease in SHBG would limit the number of androgens that could bind and be rendered inactive, thus allowing for a greater number of bioavailable androgens. This greater number of bioavailable androgens may, in turn, facilitate physiological sexual arousal.

Indeed, in a multicenter randomized controlled trial, Nathorst-Böös and Hammar (1997) found that the coadministration of estradiol and the androgenic progestin norethisterone acetate improved vaginal dryness in postmenopausal women to a greater extent than tibolone. Tibolone is an orally-administered synthetic steroid with weak estrogenic, progestogenic and androgenic properties (Kloosterboer, 2001). A review provided by the Global Consensus on Menopausal Hormone Therapy found tibolone to be an effective treatment of menopausal symptoms such as bone loss and vaginal atrophy (de Villiers et al., 2016); its use in the treatment of sexual arousal dysfunction has yielded promising results (Laan, van Lunsen, & Everaerd, 2001; Nathorst-Böös & Hammar, 1997; Nijland et al., 2008). Similarly, a meta-analysis examining the effect of OCP use on SHBG and androgen concentrations found that second-generation progestins, which are notoriously androgenic, were associated with significantly lower levels of SHBG production and significantly greater levels of androgen concentration than other generations of progestins (Zimmerman et al., 2014).

In addition to influencing sexual function through altering serum SHBG concentrations, supraphysiological quantities of certain progestins may also alter the structure of vaginal tissue. A recent, prospective study found that women had decreased thickness of the labia minora, reduced diameter of the vulvar vestibule, and reduced clitoral

blood flow after three months of receiving an OCP containing the antiandrogenic progestin drospirenone (Battaglia et al., 2012). It, therefore, appears as though certain progestins may influence sexual function indirectly through the moderation of various effects of exogenous estrogens, or directly through alteration of the structure of the vaginal tissue.

CHAPTER 2: THE PRESENT STUDY

2.1. BRIEF OVERVIEW

The present study examined the effect of exogenous sex steroid hormones on physiological sexual arousal in women. Women taking hormonal contraceptives containing low doses of ethinylestradiol coupled with either an androgenic or antiandrogenic progestin were recruited from the local community. Women with no history of having used hormonal contraceptives were also recruited and served as a control group. Participants' physiological sexual arousal in response to erotic films was assessed in two ways. Genital blood flow was measured with a vaginal photoplethysmograph, and vaginal lubrication was measured with the Schirmer Tear Test strips (Handy & Meston, 2018a). Results from these physiological measures were then compared across groups of women. A small blood sample (4.0 mL) was collected for quantification of sex hormone binding globulin (SHBG) to examine its potential mechanistic role within these relationships. In order to determine whether psychological measures of sexual arousal varied across groups, participants also provided self-report ratings of subjective sexual arousal and perceived genital arousal in response to the erotic films. Participants also provided self-report ratings of sexual function and demographic variables. This is the first study to quantify variations in physiological lubrication by oral contraceptive use.

2.2. SPECIFIC AIMS AND HYPOTHESES

Aim 1: To test for differences in genital blood flow and vaginal lubrication among women using oral contraceptive pills with various androgenic properties. I hypothesized that women taking oral contraceptive pills (OCPs) containing low (≤25 μg) doses of

ethinylestradiol coupled with an antiandrogenic progestin would exhibit a poorer sexual arousal response compared to women taking OCPs containing low (≤25 μg) doses of ethinylestradiol coupled with an androgenic progestin. I also hypothesized that women in the control group (i.e., who were not using hormonal contraceptives) would exhibit the greatest sexual arousal response.

Given the varying androgenic qualities of different progestins (Regidor, 2014), certain progestins may be more likely than others to interfere with healthy sexual function. I hypothesized that women taking OCPs with antiandrogenic progestins would have poorer physiological sexual arousal compared to those taking OCPs with androgenic progestins or control women for two primary reasons. First, progestins combat the estrogen-induced increase in SHBG to varying degrees based on the androgenic properties of the progestin. Specifically, androgenic progestins have been linked with the *least* amount of increase in SHBG, and antiandrogenic (or minimally androgenic) progestins have been linked with the *highest* increase in SHBG (Zimmerman et al., 2014). For example, the second generation androgenic progestin levonorgestrel has been found to increase SHBG production ~50%, whereas the third generation antiandrogenic progestin Desogestrel has been found to increase SHBG production ~250% (Zimmerman et al., 2014).

Second, antiandrogenic progestins have been linked with structural decrements of the genitals. For example, Battaglia and colleagues (2012) found decreased thickness of the labia minora, reduced diameter of the vulvar vestibule, and reduced clitoral blood flow after three months of receiving an OCP containing the antiandrogenic progestin drospirenone. These structural changes mimic that which is seen during menopause. Given

the high prevalence of sexual concerns that onset at menopause (Dennerstein, Alexander, & Kotz, 2003) and the large body of literature linking hormonal changes to these sexual concerns (as reviewed in Bachmann & Leiblum, 2004), it was anticipated that physiological sexual arousal would be most impaired in women taking OCPs containing an antiandrogenic progestin. Similarly, physiological sexual arousal was anticipated to be least impaired (i.e., the strongest) in women who were not using any form of hormonal contraception.

Aim 2: To examine the mechanistic role of SHBG in the relationship between genital blood flow and lubrication and oral contraceptive use. Increased serum concentrations of SHBG results in fewer bioavailable androgens (Zimmerman et al., 2014), and androgens are critical to healthy female sexual arousal (Davis et al., 2016). This may lead to decreased stimulation of androgen receptors within the vaginal tissue, thus decreasing vaginal blood flow and subsequent lubrication. It was hypothesized that women taking OCPs containing antiandrogenic progestins (i.e., progestins that facilitate SHBG production) would exhibit poorer physiological sexual arousal responses compared to women who were taking androgenic OCPs or women in the control group (i.e., those who are not taking and never have taken OCPs).

Aim 3: To test for differences in measures of subjective sexual arousal among women using oral contraceptive pills with various androgenic properties. In contrast to Aim 1, I hypothesized that measures of subjective sexual arousal would be relatively similar across the three groups of women. Much research has shown that women tend to have low and variable relationships between their subjective and genital arousal response

(see Chivers et al., 2010, for a review), though these relationships may vary slightly by methodology and statistical approach (e.g., Handy, Stanton, Pulverman, & Meston, 2018).

Researchers have proposed that women's experience of subjective sexual arousal is influenced by a multitude of factors in addition to genital arousal (Meston & Stanton, 2018). For example, contextual factors such as relational and partner-specific variables have been identified as important aspects of women's self-reported experiences of sexual arousal (Graham, Sanders, Milhausen, & McBride, 2004; Handy, Stanton, & Meston, 2018). Similarly, individual differences analyses have found that women's views of their sexual selves (Clifton, Seehuus, & Rellini, 2015) and the tendency to pay attention to bodily sensations (Velten & Brotto, 2017) significantly influence the relationship between women's subjective and genital sexual arousal. It is, therefore, possible that one's physiological response may be hindered by an OCP while their subjective arousal response is not. Indeed, the one study to examine changes in physiological and subjective sexual arousal in women before and after beginning an OCP regimen found no changes in subjective sexual arousal despite finding slight decreases in physiological arousal (Seal et al., 2005). I, therefore, expected that subjective sexual arousal would be similar across the three groups of women.

Aim 4: To test for differences in perceived genital arousal among women using oral contraceptive pills with various androgenic properties. Similar to Aim 1, I hypothesized that women taking OCPs containing low (≤25 μg) doses of ethinylestradiol plus an antiandrogenic progestin would exhibit lower levels of perceived genital arousal compared to women who were taking OCPs containing low (≤25 μg) doses of ethinylestradiol

coupled with an androgenic progestin. Women in the control group (i.e., who were not using hormonal contraceptives) were anticipated to report the greatest amount of perceived genital arousal. Despite some suggestions that women are unaware of their genital arousal response (e.g., Basson, 2002), more recent research has found that, when measured continuously as opposed to using a Likert scale rating, women are able to accurately report changes in genital blood flow (Handy & Meston, 2016, 2018b). Therefore, it was expected that physiological differences among the three groups of women would also be evidenced in self-report measures of perceived genital arousal.

Aim 5: To explore differences in sexual function among women using oral contraceptive pills with various androgenic properties. I hypothesized that women taking OCPs containing low (≤25 μg) doses of ethinylestradiol plus an antiandrogenic progestin would report the lowest levels of sexual function. I did not expect there to be any large, overwhelming differences in sexual function between women taking low (≤25 μg) doses of ethinylestradiol coupled with an androgenic progestin and women in the control group. I believed it would be likely that, for the majority of women, the physiological effects observed in Aim 1 would not be indicative of a sexual dysfunction per se. Rather, the effects observed in the present study may reflect pre- or subclinical sexual arousal concerns.

Lower levels of sexual function (but not yet sexual dysfunction) were hypothesized to be most likely to occur in the group of women taking OCPs containing low (≤25 μg) of ethinylestradiol plus an antiandrogenic progestin as this composition is believed to have the most profound effect on physiological sexual arousal. The effect of the OCP containing

low (≤25 μg) doses of ethinylestradiol coupled with an androgenic progestin was hypothesized not to be strong enough to translate to sexual function that differed significantly from that of women in the control group.

CHAPTER 3: EXPERIMENTAL DESIGN, MATERIALS, AND METHODS

3.1. EXPERIMENTAL DESIGN

This study included a clinical interview and a single experimental session. During the experimental session, participants viewed two different neutral and erotic film clips while their physiological and subjective sexual arousal responses were measured. Two forms of physiological sexual arousal were measured: vaginal lubrication and genital blood flow. One form of physiological sexual arousal was measured during each film. The form of measurement and films were counterbalanced across study sessions. Subjective sexual arousal and perceived genital arousal were measured in relation to each film. The study session concluded with the completion of several self-report questionnaires pertaining to sexual health and, for a random sampling of women, a small (4.0 mL) blood draw.

3.2. PARTICIPANTS

Participants included in the present study were 130 adult, premenopausal, women who were either currently taking or had never taken oral contraceptive pills (OCPs) at the time of participation. Effort was made to recruit women evenly across the following three groups, however, considerably fewer women reported taking antiandrogenic OCPs, thus leading to a notably smaller group size:

Group 1: Low-dose ethinylestradiol plus androgenic progestin (n = 50)

Group 2: Low-dose ethinylestradiol plus antiandrogenic progestin (n = 21)

Group 3: Non-hormonal contraceptive control (n = 59)

Participants were recruited through online advertisements and flyers posted throughout the local community (e.g., in laundromats, coffee shops, public bathrooms), as

well as through the Human Subjects Pool in Psychology at the University of Texas at Austin. These advertisements included basic information regarding inclusion criteria, time commitment, and compensation provided. Separate advertisements were created to target women who were and were not taking OCPs. All advertisements invited women to call the laboratory for a phone eligibility screening, and then if eligible, women were invited to schedule a clinical interview and experimental session. As OCPs mimic the body's natural post-ovulatory hormonal concentrations (Rivera et al., 1999), all naturally-cycling women were scheduled to participate in the laboratory session during the luteal phase (i.e., between days 14 and 28) of their menstrual cycle. This also served as a method of gaining conservative estimates of possible between-group differences, as greater levels of sexual function are typically observed during the follicular phase of women's menstrual cycles (S. G. Brown, Calibuso, & Roedl, 2011; Caruso et al., 2014; Clayton, Clavet, Mcgarvey, Warnock, & Weiss, 1999; Dawson, Suschinsky, & Lalumière, 2012; Graham, Janssen, & Sanders, 2000).

3.2.1. Inclusion and Exclusion Criteria

3.2.1.1. Inclusion Criteria:

1. *At least 18 years of age.* We did not include women under 18 in this study because of ethical issues concerning the exposure of minors to sexually explicit content, and viewing the sexual films was inherent to study participation.
2. *Fluent in English.* Participants were required to be fluent in English as the majority of the self-report measures are only available in English and there are not yet appropriate alternative instruments. For consistency across participation

experiences, the use of translators was not offered to potential non-English-speaking participants.

3. *Currently sexually active*. As the Female Sexual Function Index (Rosen et al., 2000) was validated for use in women who are currently sexually active, it was required that those who participated in this study had engaged in sexual activity within the past four weeks. In order to increase the number of women who were considered sexually active, the definition of sexual activity was expanded to include deep kissing and petting, as well as partnered or solitary sexual activity.
4. *Currently taking an OCP <u>OR</u> no history of taking any hormonal contraceptives.* Women who qualified for the low-dose ethinylestradiol plus androgenic progestin were required to be taking an OCP containing ≤25 μg of ethinylestradiol coupled with an androgenic progestin. Women who qualified for the low-dose ethinylestradiol plus antiandrogenic progestin were required to report taking an OCP containing ≤25 μg of ethinylestradiol coupled with an antiandrogenic progestin. The androgenicity of a progestin was calculated using Dickey's (Dickey, 2000) classification of androgenic activity, using a .5 threshold cutoff. Preference was given to first and second generation progestins for being classified as androgenic, whereas preference was given to third and fourth generation progestins for being classified as antiandrogenic. Refer to Table 1 for an index of commonly used progestins and their relative androgenic activity.

Table 1.

An Index of the Relative Androgenic Activity of Various Progestins Found Within Common Oral Contraceptive Pills

Progestin (1 mg)	**Relative Androgenicity**
Norethindrone	1.0
Norethrindrone acetate	1.6
Ethynodiol diacetate	0.6
Levonorgestrel	8.3
Norgestrel	4.2
Norgestimate	1.9
Norelgestromin	1.9
Desogestrel	3.4
Drospirenone	0.0

Note: mg = milligram. The androgenic activity for each progestin is relative to 1 mg of norethindrone. For example, the progestin levonorgestrel is 8.3 times more androgenic than is norethindrone. Chart adapted from Dickey (2000).

To allow the body to adjust to changes in hormone concentrations, it was further required that women in both contraceptive groups had been taking their OCP for at least 3 months to qualify for participation (see Battaglia et al., 2012, for documentation of vaginal changes after 3 months of OCP use). Furthermore, in order to identify whether specific progestin doses contributed to any between-group

differences in sexual arousal, it was required that the OCPs included in this study were monophasic (i.e., the dose remained the same for each week of active pills). Women who qualified for the non-hormonal contraceptive control group must have reported no history of ever having used a hormonal contraceptive. See Table 2 for a sample list of OCPs and their composition as it relates to each of the two OCP groups in this study.

Table 2.

Sample List of Oral Contraceptive Pills and Compositions for Each of the Three Study Groups

Group	Brand Name	Estrogen Dose (mg)	Progestin	Progestin Dose (mg)	Androgenicity
Low-dose Ethinylestradiol + Androgenic Progestin	Afirmelle	0.020	Levonorgestrel	0.10	0.83
	Aurovela Fe	0.020	Norethindrone acetate	1.00	1.60
	Kaitlib Fe	0.025	Norethindrone	0.80	0.80
	Lo Lestrin Fe	0.010	Norethindrone	1.00	1.00
	Taytulla	0.020	Norethindrone	1.00	1.00
Low-dose Ethinylestradiol + Anti-Androgenic Progestin	Gianvi	0.020	Drospirenone	3.00	0
	Loryna	0.020	Drospirenone	3.00	0
	Micrette	0.020	Desogestrel	0.15	0.50
	Nikki	0.020	Drospirenone	3.00	0
	Yaz	0.020	Drospirenone	3.00	0

Note: mg = milligram. All oral contraceptive pills listed in the above Table contain the synthetic estrogen ethinylestradiol.

3.2.1.2. Exclusion Criteria:

1. *Over 35 years of age*. Only women between the ages of 18 and 35 were included in this study in an attempt to increase sample homogeneity. There is a large body of literature indicating sexual function declines with age (Hayes & Dennerstein, 2005), with a specific, negative effect of menopause on sexual desire, arousal, lubrication and pain (Dennerstein et al., 2003). The upper limit of age was set at 35 because I was interested in studying changes in sexual arousal that are associated with OCP use rather than sexual dysfunction associated with medical and clinical conditions linked to age.
2. *Pregnant or breastfeeding*. Sexual function is affected by the physiological and hormonal changes that occur as a result of pregnancy, and these changes persist into the postpartum period (Serati et al., 2010). Therefore, women who fit this criterion were excluded from participation in the present study.
3. *Currently taking beta blockers, antidepressants, anxiolytics, antipsychotics, or any medical treatments to enhance sexual response.* All of these medications have been shown to have sexual side effects (Rosen & Kostis, 1985; Serretti & Chiesa, 2009; Stuckey, 2008), which can alter physiological and psychological sexual arousal. Therefore, women reporting the use of any of these medications were excluded from participation.
4. *Currently receiving exogenous hormones or hormone precursors (e.g., dehydroepiandrosterone) other than those provided by the OCP*. In an effort to

isolate the effects of the hormones provided by the OCP, women receiving additional exogenous hormones were not eligible to participate.

5. *Currently experiencing stress or urinary incontinence*. The additional liquid within the vaginal area due to stress or urinary incontinence can interfere with the measurement of vaginal lubrication. Therefore, women with either of these conditions did not qualify for participation in this study.
6. *History of a medical condition known to affect hormone function.* Similar to above, in an effort to isolate the effects of the hormonal OCP, women with a history of a medical condition known to affect hormone function (e.g., hyper- or hypothyroidism, adrenal hyperplasia, polycystic ovarian syndrome) were deemed not eligible to participate in this study.
7. *History of major pelvic surgery that caused nerve damage.* Women with pelvic nerve damage have significantly different patterns of sexual arousal from those without such damage (Vlug et al., 2010). In an effort to eliminate additional sources of variability from our study, we excluded from participation women with a history of major pelvic surgery (e.g., hysterectomy, vulvectomy, or serious rectal, bladder, or abdominal surgery) that resulted in nerve damage.
8. *History of childhood sexual abuse.* Childhood sexual abuse was defined as unwanted oral, anal or vaginal penetration, or genital touching or fondling before age 16 (Rellini, 2008). A large body of literature indicates that childhood sexual abuse has negative effects on women's sexual health (e.g., Rellini & Meston, 2007).

Therefore, women with such histories were excluded to reduce variability in our data.

9. *History of Sjögren's or related syndromes*. Sjögren's syndrome is an autoimmune disease that causes dryness in the body, including the vaginal area (Bongi, Rosso, Orlandi, & Matucci-Cerinic, 2013). As the aim of the present study was to examine differences in vaginal lubrication across groups of OCP users, women who experienced difficulties with vaginal lubrication due to Sjögren's or a related syndrome were excluded.

3.2.2. Final Participant Sample

The sample of 130 women participating in this study satisfied the recommended sample size for achieving adequate statistical power. Of the 466 women who called the Female Sexual Psychophysiology Laboratory to inquire about the study, 37 women were no longer interested in participating after learning more about the required study procedures. The remaining 429 callers were screened for eligibility, with 269 women calling from the local community and 160 seeking course credit at the University of Texas at Austin.

Of those screened, 263 callers were ineligible for a variety of reasons, including not being fluent in English (2.6%); not having engaged in any sexual activities within the past four weeks (22.4%); being younger than 18 or older than 35 years of age (4.5%); past, but not current, OCP use (17.8%); using an OCP containing >25 μg ethinylestradiol (36.8%); using a multiphasic OCP (11.0%); using a progestin-only OCP (1.9%); using additional forms of hormones (7.6%); being pregnant or breastfeeding (1.9%); reporting a history of

childhood sexual abuse (15.5%); taking beta-blockers, antidepressants, anxiolytics, or other medications known to interfere with sexual function (18.2%); having a medical condition known to affect hormone function (9.1%); reporting a history of pelvic nerve damage (1.5%); experiencing stress incontinence and/or urinary leakage (1.9%); having a history of Sjögren's syndrome or a related autoimmune disorder (1.9%). These percentages reflect the total amount of women who were ineligible due to any given criterion. Women could, and many did, be ineligible for a variety of reasons. As such, these totals do not equal 100%.

Of the remaining 166 eligible women, 36 women scheduled a visit but either canceled or did not attend their study session. The rate of nonparticipation (21.68%) in this study is fairly typical for laboratory-based sexual psychophysiological studies (e.g., Lorenz & Meston, 2014; Stanton, Boyd, Fogarty, & Meston, 2019).

3.2.3. Group Differences in Demographic Characteristics

Continuous variables (i.e., age, age of sexual debut, and relationship length) were assessed using a series of multivariate analyses of variance (MANOVA) using base R (Team, 2019). Discrete demographic variables (i.e., sexual orientation, relationship status, medication use, race, educational attainment, household income) were analyzed using chi-square tests of independence using the MASS package for support functions and datasets for Venables and Ripley's MASS (Ripley et al., 2019). Efforts were made throughout the recruitment process to match study groups on their demographic variables.

Indeed, it was found that women in the three groups did not differ significantly on any of the demographic variables included in the present study. A chi-square test of

independence indicated possible between-group differences in race, with more Asian-identified women within the control group and more Caucasian-identified women within the androgenic group ($p = .017$). This effect is documented in the literature and is believed to reflect differing cultural factors, as well as disparities in access to care and treatment (Lee, Carvallo, & Lee, 2015; Phares, Cui, & Baldwin, 2012). However, the difference observed in the present study was no longer significant after applying a Bonferroni correction for the number of comparisons ($\kappa = 9$; $\alpha/9 = 0.005$) and was therefore not controlled for in subsequent analyses.

On average, women who participated in this study were 20.12 years old ($SD = 2.53$). Three-quarters (74.61%) of the participants identified as heterosexual, and roughly half (55.38%) reported being in a committed relationship. The average relationship length was 19.26 months (i.e., roughly 1.5 years; $SD = 19.19$). The racial makeup of the participants included in this study roughly reflected that of the general Austin population, with 33.07% of the sample identifying as Caucasian, 29.23% identifying as Hispanic, 24.61% identifying as Asian, and 9.23% identifying as African American (DataUSA, 2019). Three-quarters (76.92%) of the participants reported having completed some college, and 43.84% reported a household income of less than $50,000. Refer to Tables 3 and 4 for a breakdown of the continuous and discrete demographic characteristics for each group, respectively.

Table 3.

Continuous Demographic Characteristics for Participants in Each Study Group

Demographic variable	Control *N* = 59		Androgenic *N* = 50		Antiandrogenic *N* = 21		
	M	***SD***	***M***	***SD***	***M***	***SD***	***F***
Age	19.98	3.08	20.20	1.88	20.33	2.26	0.182
Age of sexual debut	16.72	2.64	17.30	1.70	18.09	2.70	2.773
Relationship length	22.05	24.00	18.39	16.48	14.94	9.84	0.827

Note: M = mean; *SD* = standard deviation. Relationship length is calculated in months. No significant between-group differences emerged for any of these variables.

Table 4.

Discrete Demographic Characteristics for Participants in Each Study Group

Demographic variable	Control *N* = 59		Androgenic *N* = 50		Antiandrogenic *N* = 21		
	n	**%**	***n***	**%**	***n***	**%**	χ^2
Orientation							11.336
Heterosexual/Straight	42	71.18	40	80.00	15	71.42	
Bisexual	11	18.64	6	12.00	5	23.80	
Queer	2	3.38	-	-	1	4.76	
Homosexual/Gay/Lesbian	3	5.08	-	-	-	-	
Other	1	1.69	4	8.00	-	-	

Table 4 (continued).

Relationship status							12.825
Single, not dating	14	23.72	7	14.00	2	9.52	
Single, dating	14	23.72	16	32.00	2	9.52	
Committed relationship	30	50.84	25	50.00	17	80.95	
Married	1	1.69	-	-	-	-	
Other	-	-	2	4.00	-	-	
Prescription drug use							2.678
Yes	9	15.25	14	28.00	5	23.80	
No	50	84.74	36	72.00	16	76.19	
Ethnicity							2.372
Hispanic	24	40.67	14	28.00	9	42.85	
Non-Hispanic	35	59.32	35	72.00	12	57.14	
Race							18.499*
African American/Black	8	13.55	1	2.00	3	14.28	
Asian	16	27.11	13	26.00	3	14.28	
Caucasian/White	11	18.64	25	50.00	7	33.33	
Hispanic	20	33.89	11	22.00	7	33.33	
Other	4	6.77	-	-	1	4.76	

Table 4 (continued).

Religion							20.470
Atheism/Agnostic	18	30.50	21	42.00	6	28.57	
Christianity	18	30.50	7	14.00	8	38.09	
Catholicism	14	23.72	14	28.00	4	19.04	
Judaism	1	1.69	-	-	1	4.76	
Islam	-	-	3	6.00	-	-	
Spiritual/New Age	3	5.08	4	8.00	1	4.76	
Other	5	8.47	1	2.00	1	4.76	
Education							11.338
High school diploma/GED	9	15.25	3	6.00	-	-	
Some college	43	72.88	41	82.00	16	76.19	
College degree	7	11.86	4	8.00	5	23.80	
Advanced degree	-	-	2	4.00	-	-	
Household income							5.663
<$50,000	28	47.45	20	40.00	9	42.85	
$50,000-$100,000	20	33.89	12	24.00	4	19.04	
>$100,000	11	18.64	18	36.00	8	3.80	

Note: GED = General Education Diploma; MA = Master's degree.

* $p = 0.017$; insignificant after the application of a Bonferroni correction of .005

3.2.4. Nature of the Oral Contraceptive Pills Used by Study Participants

Nearly all women (*n* = 45; 90%) in the androgenic group reported currently taking OCPs containing 20 μg ethinylestradiol. Four participants (8.00%) in this group were taking OCPs with 10 μg ethinylestradiol and one (0.19%) with 25 μg ethinylestradiol. For the progestin compositions, 34 women (68.00%) in this group were taking OCPs with 1 mg norethindrone acetate. Ten women (20.00%) were taking OCPs containing 1 mg norethindrone, one participant (0.19%) was taking an OCP with .8 mg norethindrone, and four (8/00%) participants were taking OCPs containing .1 mg levonorgestrel. Ten women (20.00%) in this group reported previous use of a hormonal contraceptive with a different hormonal composition than their current OCP.

One woman (4.76%) taking antiandrogenic OCPs reported taking an OCP containing 25 μg ethinylestradiol. The remaining women (*n* = 20; 95.23%) reported using an OCP with 20 μg ethinylestradiol. With regards to progestin use, the majority of women (*n* = 13; 61.90%) were taking an OCP containing 3 mg drospirenone. Seven participants (33.33%) were taking an OCP with .15 mg desogestrel and one participant (4.76%) was taking an OCP with 35 μg norgestimate. Half of the women (*n* = 11; 52.38%) in this group reported previous use of hormonal contraceptives containing a different composition of hormones.

3.3. Equipment and Measures

3.3.1. Clinical Interview

All participants underwent a brief clinical interview to gather information regarding their contraceptive use history (Appendix A) and determine the presence or absence of

sexual arousal concerns. During this, the women took part in a brief clinician-administered screener, the Female Sexual Dysfunction Diagnosis (FSDD), which based on DSM-IV-TR female sexual arousal disorder criteria (Appendix B). The FSDD comprises a series of questions regarding their current ability to become sexually aroused. This is to determine whether their sexual concern (if present) is arousal-specific, as the present study focused specifically on women's sexual *arousal* response. These questions examine: a) whether women had ever experienced a series of genital sensations; b) the extent to which women experience these sensations during sexual activity; c) whether this is situational in nature; d) the length of time they have been experiencing this difficulty; e) whether they self-identify as having an arousal problem; and f) if they are distressed by this problem. Women in both of the OCP groups were also asked whether they attributed any of these symptoms to their prescribed OCP.

3.3.2. Manipulation: Neutral and Erotic Videos

The experimental stimuli consisted of four 10-minute film presentations that were each composed of a 4-minute neutral clip and a 6-minute erotic clip. The neutral clips were comprised of a 1-minute display of the text "Relax" followed by a 3-minute panoramic nature scene. Two of the erotic clips depicted a mixed-sex couple and two clips depicted a same-sex couple engaging in sexual activity. Women were allowed to select whether they preferred to watch either the mixed- or same-sex films. The erotic clips progressed from two minutes of foreplay to two minutes of oral sex to two minutes of vaginal penetration. The four 10-minute films were matched for content and presented to women in a randomized order. These clips were selected from sexual videos produced and directed by

women because past studies indicated that these videos are more successful at producing both physiological and subjective sexual responses in women (Laan, Everaerd, van Bellen, & Hanewald, 1994). Past studies that used these videos found significant increases in women's physiological and subjective sexual arousal (Handy & Meston, 2016, 2018b).

3.3.3. Laboratory-Based Measures

3.3.3.1. Physiological Arousal

3.3.3.1.1. Genital blood flow

A vaginal photoplethysmograph was used to assess women's genital blood flow in response to the film presentations. The vaginal pulse amplitude (VPA) signal was sampled at a rate of 200 samples per second throughout the entire 240 seconds of neutral film presentation and 360 seconds of erotic film presentation. Each wave was recorded in millivolts, band-pass filtered (0.5-30 Hz), and recorded on a computer in the next room using the software program AcqKnowledge III, Version 3.8.1 and a Model MP150 data acquisition unit (BioPac Systems, Inc., Santa Barbara, CA, USA) for analog and digital conversion. To ensure that the phototransistor was inserted at the correct depth and orientation for each participant, a positioning shield was attached to the cord of the vaginal photoplethysmograph. Once the photoplethysmograph was inserted, women were asked to slide the positioning shield towards their body until it rested against their vulva.

3.3.3.1.2. Vaginal lubrication

Lubrication was measured with the Schirmer Tear Test strips, a test which previous research has shown to be sensitive enough to detect changes in vaginal lubrication induced by sexual films (Handy & Meston, 2018a). The test strips are ruled in millimeter

increments and are 40 millimeters in length. In this assessment, a paper test strip is applied directly to the vaginal membrane, and the amount of moisture absorbed into the test strip is measured. In an attempt to standardize the depth of insertion of these test strips, they were adhered to wooden applicators beginning at five millimeters, thus allowing for only the first five millimeters to be inserted into the vaginal opening consistently across participants.

To avoid transference of moisture from the labia to the test strip, women were instructed to part their labia with one hand. Using a standing, adjustable mirror as a guide, women then inserted the test strip with their free hand until they felt the tip of the wooden applicator touch their vaginal skin. This was done to ensure that the test strips were inserted at a standardized depth (i.e., five millimeters) and location (i.e., 6 o'clock) for each woman.

Women held the test strip in place for 60 seconds. At 60 seconds, women were instructed to remove the test strip, place it in a plastic bag, and cover up with a drape provided by the experimenters. When alerted that the participant is covered, an experimenter entered the room to obtain the plastic bag and test strip. Immediately after leaving the participant's room and returning to the experimenter's room, two experimenters independently recorded the length of moisture absorbed into the test strip. To minimize potential bias, experimenters running the study sessions were blind to the contraceptive method used by the participants. To account for unaroused (i.e., baseline) levels of vaginal moisture and capture lubrication that was produced in response to the erotic film, this procedure was conducted immediately before and after watching one of the film presentations.

3.3.3.2. Subjective Arousal

3.3.3.2.1. Continuous Subjective Sexual Arousal

Subjective sexual arousal was measured continuously during each film presentation with an arousometer (Rellini et al., 2005). The arousometer is a computer mouse attached to a lever ranging from 0 to 7, that the participant moves throughout stimuli presentation to indicate their perceived level of physiological arousal. The device was positioned on a small table at the side of the participant's chair. Each participant began with the lever at 0 and was instructed to move the mouse to indicate changes in subjective sexual arousal. Specifically, they were instructed: "Please move the mouse to indicate any changes in your mental sexual arousal, or how turned on you feel in your mind." The position of the *y*-axis of the mouse was recorded every 0.50 seconds on a computer in the next room using the scripting program MatLab 2013b (MathWorks, 2013). The arousometer has been validated for use in capturing changes in subjective arousal during exposure to an erotic stimulus (Rellini et al., 2005).

3.3.3.2.2. Discrete Subjective Sexual Arousal

The majority of laboratory-based studies examining women's subjective sexual arousal ask participants to complete questionnaires at the beginning and end of the film presentation. In order to compare the results of the present study to the extant literature, a similar measure was administered (Appendix C). The Film Scale (Heiman & Rowland, 1983) is a 41-item measure that has five subscales: genital arousal, autonomic arousal, subjective sexual arousal, negative affect, and positive affect. The Film Scale has been used in over 200 sexuality studies since its introduction in 1983, and it is frequently adapted to

meet the needs of a given study or laboratory. Though these changes preclude the use of reliability or validity statistics, the Film Scale is the measurement of choice for many researchers. In the present study, the subjective sexual arousal subscale was used as a discrete measure of this construct.

The subjective sexual arousal subscale, which was used for the discrete measurement of this construct, consists of the following three items: "sexual arousal," "mental sexual arousal" and "sexually turned off," where the latter item is reverse scored. Items are rated on a 7-point Likert scale ranging from 1 (not at all) to 7 (intensely). Total scores are summed (range: 3 – 21), with greater scores indicated greater levels of subjective sexual arousal.

3.3.3.2.3. Perceived Genital Arousal

Perceived genital arousal was assessed via five items on the Film Scale (Heiman & Rowland, 1983; Appendix C). The perceived genital arousal subscale consists of the items genital "warmth," "wetness/lubrication," "pulsing/throbbing," "tenseness/tightness," and "any genital feeling." Items are rated on a 7-point Likert scale ranging from 1 (not at all) to 7 (intensely). Item responses for this subscale are summed (range: 5 - 35), with greater scores indicating greater levels of perceived genital arousal.

3.3.4. Serum Collection

Participants underwent a small blood draw collected from the cubital vein in the supine position. Four milliliters were drawn into serum separating tubes and were then stood upright for 30 to 60 minutes to allow for optimal clotting. Samples were centrifuged for 15 minutes at 2,200 to 2,500 revolutions per minute. Upon separation, the separated

layer of blood serum was aliquoted. In a new plastic transport tube, samples were frozen at -80°C until all data were collected and ready for batch analysis performed by Wisconsin National Primate Research Center (see Stroud et al., 2007, for an assessment of the stability of sex steroid hormones and binding globulins over time). Sex hormone binding globulin serum concentrations were measured using commercial enzyme-linked immunosorbent assay (ELISA) in nanomoles per liter (nmol/L). This form of assay uses a solid-phase enzyme immunoassay to detect the presence of a protein in a sample using antibodies directed against that protein.

3.3.5. Psychological Measures

3.3.5.1. Demographics

Demographic characteristics were assessed with a questionnaire on age, age of sexual debut, sexual orientation, relationship status, relationship length, medication use, race, educational attainment, and household income (Appendix D). These data were used to assess for differences between participant groups in an effort to balance these background characteristics across groups.

3.3.5.2. Contraceptive Side Effects

Women (except for those in the non-hormonal contraceptive control group) were provided with an author-constructed list of common side effects of oral contraceptive pills and were asked to endorse any symptoms they experienced over the past three months (Appendix E). These self-reported data were used to compare both sexual (e.g., changes in sexual desire) and nonsexual (e.g., changes in weight) side effects between the two groups.

Items are scored in binary, with 1 reflecting the presence of a given symptom and 0 reflecting the absence.

3.3.5.3. Sexual Function

To assess participants' level of sexual function on a continuous scale, women completed the Female Sexual Function Index (FSFI; Rosen et al., 2000), which is a 19-item self-report questionnaire that assesses the six domains of women's sexual function (desire, arousal, lubrication, orgasm, satisfaction, and pain), as well as overall sexual functioning (Appendix F). Total scores range from 1.2 to 36, where poorer sexual function is represented by lower scores. The FSFI has been found to have good internal reliability (r = 0.89-0.97), test-retest reliabilities (α = 0.79-0.88), and has confirmed discriminant validity in distinguishing women with sexual complaints from women without those complaints (Rosen et al., 2000; Ryding & Blom, 2015; Wiegel, Meston, & Rosen, 2005). Because we anticipated the participation of lesbian and bisexual women in this study, the instructions of the FSFI were modified to avoid heterosexual tendencies (i.e., exclusive references to penile penetration of the vagina), and were replaced with generic references to vaginal penetration.

3.3.5.4. Sexual Distress

The Female Sexual Distress Scale-Revised (FSDS-R; DeRogatis, Clayton, Lewis-D'Agostino, Wunderlich, & Fu, 2008) was used to measure participants' levels of sexual distress. The FSDS-R is a 13-item self-report questionnaire assessing sex-related distress (Appendix G). Items are rated on a 5-point Likert scale ranging from 0 (never) to 4 (always). Total scores on the FSDS-R range from 0 to 52, with higher scores indicating

greater distress. The FSDS-R has been shown to have good discriminant validity in differentiating between women with and without hypoactive sexual desire disorder, satisfactory internal consistency (>0.88 for groups of women with various sexual dysfunctions), and test-retest reliability (0.88; Derogatis et al., 2008).

3.3.5.5. Vulvar and Vaginal Atrophy

Symptoms of vulvar and vaginal atrophy were assessed with a 5-item measure that is commonly implemented in Food and Drug Administration trials assessing vaginal health (Appendix H). In this measure, participants rate the severity of the following symptoms on a 4-point Likert-type ranging from 0 (mild) to 3 (severe): vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, and vaginal pain associated with sexual activity. Participants also dichotomously rate the presence or absence of vaginal bleeding associated with sexual activity.

3.3.5.6. Positive Sexuality Survey

This author-constructed survey assesses how confident, satisfied, and pleased women are with their experience of vaginal lubrication and sexual activity (Appendix I), and the scale was developed specifically for the purpose of this dissertation. On this measure, participants are instructed to rate the extent to which they agree with the five statements on a scale of 1 (strongly disagree) to 6 (strongly agree), where higher scores indicate a more positive experience of sexual activity. Participants are also asked to rate these questions based on their experiences over the past four weeks. Items are summed, and total scores for this measure range from 5 to 30. The Positive Sexuality Survey has yet to be validated for use in women, though should still provide researchers with a sense of

how confident women are in their sexual arousal responses. The wording and structure of this questionnaire were modeled after the FSFI (Rosen et al., 2000).

3.4. PROCEDURE

3.4.1. Determining Eligibility

Interested participants contacted the laboratory and spoke with a trained research assistant who provided standardized information regarding the study and answered any questions that were raised. Participants were offered the opportunity to complete a confidential phone screen to review the inclusion and exclusion criteria. Women who were deemed eligible after completing the phone screen were invited to schedule a clinical interview and experimental session and were e-mailed a link to the study's electronic Informed Consent Document.

3.4.2. Clinical Interview

Participants who agreed to participate in this study and electronically signed the Informed Consent Document completed a brief clinical interview either via telephone or in-person, based on the participant's preference. During the interview, women's level of sexual function was assessed to determine the presence or absence of a sexual desire and/or arousal dysfunction. Women were then asked about relevant OCP use (e.g., how long they had been taking their current OCP, if they had taken different OCPs in the past). The screening for sexual dysfunction occurred prior to assessing OCP use in an attempt to reduce the possibility of clinician bias. Thus, the clinician was blind to the OCP status of the participants while screening for sexual dysfunction. On average, the clinical interview was about 30 minutes in duration.

3.4.3. Experimental Session

Individual study sessions were conducted for each participant. Upon arrival to the laboratory, participants received an explanation of all study procedures and instruments, and they were be allowed the opportunity to ask any questions that they had. Women then received a labeled diagram of the vulvar region and detailed instructions on how to perform the lubrication measurement, insert the vaginal photoplethysmograph, and attach electrocardiogram electrodes. Participants then took part in the first measure of sexual arousal. As it is presently unknown whether inserting the vaginal photoplethysmograph could interfere with the measure of lubrication, lubrication and VPA were measured in response to two separate film presentations. Participants were randomly assigned to the order in which their physiological arousal was measured (i.e., lubrication followed by VPA, or VPA followed by lubrication). Film order and measure of physiological arousal were counterbalanced across participants, and, to minimize the possibility of researcher bias, the experimenters were blind to the form of OCP (i.e., androgenic or antiandrogenic, if any) used by each participant.

During the films, participants were instructed to continuously move the arousometer to indicate their level of subjective sexual arousal. The two film presentations were separated by a 5-minute rest period to allow participants' arousal to return to baseline. During the rest period, women were instructed to read National Geographic's *Inside Animal Minds* (Keim, 2017) magazine provided by the experimenters. This magazine was selected to reduce participants' exposure to images of people during the rest period, as

nonsexual images of people have been shown to increase genital arousal in some instances (as reviewed in Lalumière, Sawatsky, Dawson, & Suschinsky, 2020).

Those who participate in the VPA session prior to the lubrication session were asked to gently dry their genitals with a tissue to remove any residual lubrication produced from the first film. After completing both measures of sexual arousal, the participants were asked to get dressed and complete the final set of demographic and self-report surveys. They then underwent a blood draw by a registered nurse or licensed phlebotomist hired by Clinical Pathology Laboratories. Upon completion, participants were debriefed and compensated with $20.00 (for women recruited through the community) or course credit (for women recruited through the Human Subjects Pool) for their time. On average, the entire study session lasted about 120 minutes. Refer to Figure 2 for depictions of the two counterbalanced conditions to which women were randomized.

Counterbalance Order 1:

Consent	Attach ECG, probe	Film, surveys	Detach ECG, probe	Read magazine	Lubri-cation measure	Film, surveys	Lubri-cation measure	Surveys	Blood draw	Debrief
15 min	5 min	15 min	1 min	5 min	1 min	15 min	1 min	35 min	20 min	5 min

Counterbalance Order 2:

Consent	Lubri-cation measure	Film, surveys	Lubri-cation measure	Read magazine	Attach ECG, probe	Film, surveys	Detach ECG, probe	Surveys	Blood draw	Debrief
15 min	1 min	15 min	1 min	5 min	5 min	15 min	1 min	35 min	20 min	5 min

Figure 2. Participants were randomized to one of these two counterbalanced sessions.

3.4.4. Subject Flow

Recruitment for this study took about 1.25 years (October 2018 through December 2019). The target sample size for this study was 150 women (50 per group), and it is common practice to recruit slightly more than that in case some participants fail to provide complete data. With the goal of recruiting 165 women for this study (55 women per group), roughly 10 women needed to complete the experimental session per month for the full 1.25 years. Data collection from previous studies conducted within the Female Sexual Psychophysiology laboratory suggested that this pace was ambitious but feasible. I, therefore, worked with gynecologists and primary care providers in the local community to facilitate participant recruitment. Ultimately, I recruited and ran 130 women through the complete study protocol, with 59 women in the control group, 50 women in the androgenic group, and 21 women in the antiandrogenic group.

CHAPTER 4: DATA ANALYSIS

4.1. DATA CLEANING AND REDUCTION

Vaginal pulse amplitude data were exported from AcqKnowledge 3.9.3 (BIOPAC Systems, Inc, CA) to Microsoft Excel for processing. Movement artifacts in the data were identified and removed by an automatic processing procedure that has been shown to effectively remove outliers and provide results that are comparable to visual inspection (Pulverman, Meston, & Hixon, 2018). This automatic processing procedure was conducted within the R environment (Team, 2019) using the mgcv package for generalized additive modeling (Wood, 2011). As described in Pulverman, Hixon, and Meson (2015), the procedure calculates the mean and standard deviation of each participant's heart rate and conducts an outlier test on the time between successive beats. The outliers reflect movement artifacts in both the heart rate and vaginal pulse amplitude (VPA) data and are therefore removed from the data file.

The remaining, valid heart rate data are used to identify the highest VPA value between heart rate peaks (i.e., the VPA peaks). Once the VPA peaks are identified, the procedure uses a standard, generalized cross-validated smoothing spline to create a smooth trajectory through the VPA data. Using z-scored residuals, probability estimates are calculated each data point to determine the presence or absence of movement artifacts within the VPA data. Movement artifacts are removed from the data file and the data is modeled again. This process continues until all significant artifacts are removed. The remaining data were then binned in 5-second epochs representing mean peak-to-peak VPA response, yielding a total of 120 data points per participant.

The continuously collected subjective sexual arousal data (i.e., via the arousometer) were exported from MatLab 2013b (MathWorks, 2013) to Microsoft Excel for processing. The subjective sexual arousal data were then binned in 5-second epochs, yielding a total of 120 data points per film per participant.

4.2. Statistical Analyses

4.2.1. Test of Potential Confounding Variables

All study analyses were conducted in R 3.2.3 (Team, 2019). Prior to testing the main study hypotheses, possible differences in background characteristics between the three participant groups were assessed. As stated above, no demographic variables varied significantly between groups and thus were not included in subsequent models as covariates (i.e., controlled for by holding constant; see Section 3.2.3.).

4.2.2. Test of Major Study Hypotheses

Aim 1: To test for differences in genital blood flow and vaginal lubrication among women using oral contraceptive pills with various androgenic properties.

Aim 1, Part 1: To test for differences in genital blood flow. Using the nlme package (Pinheiro, Bates, DebRoy, Sarkar, & Team, 2017) for linear and nonlinear mixed effects, growth curve modeling was implemented to examine the extent to which participants' genital blood flow changed over time. If a significant change in blood flow over time emerged, group membership (i.e., low-dose ethinylestradiol plus androgenic progestin, low-dose ethinylestradiol plus antiandrogenic progestin, and control) was to be entered into the equation as a moderator. Growth curve modeling is a modeling technique that conducts within-subject analyses of the relationships between predictor and outcome variables and

uses the products (i.e., coefficients) as outcome variables for use in between-subject analyses. That is, growth curve modeling analyzes data with regards to *individual growth*. This is particularly useful when examining VPA as baseline VPA varies from woman to woman, and growth curve modeling allows for each participant to serve as her own control. In this study, all equations were modeled with repeated measures. Additionally, the slopes and intercepts were entered as random, thus allowing them to vary across participants (Baayen, Davidson, & Bates, 2008). A model used to test the relationship between VPA and time was based on the following formula:

$$Y(VPA)_{ij} = \beta_0 + \beta_1(time)_{ij} + r_{ij}$$

where $Y(VPA)_{ij}$ is the $_i$th participant's VPA at the $_j$th time point, allowing for the assessment of VPA across participants and time. In this example, β_0 is the participant-specific intercept, β_1 is the participant-specific slope, and r_{ij} are the residuals. Time is treated as a Level 1 (or *inter-individual*) variable in this model as it varies within and not between participants.

If a significant relationship emerged, an additional analysis was to be conducted to determine if group membership moderated this relationship. The mixed model containing group membership as a moderator was as follows:

$$Y(VPA)_{ij} = \beta_0 + \beta_1(time)_{ij} + \beta_2(group)_i + \beta_3(time*group)_{ij} + r_{ij}$$

where $\beta_2(group)_i$ is the categorical demarcation of group membership for the $_i$th participant and has three values representing group membership (0 = control; 1 = low-dose ethinylestradiol plus androgenic progestin; 2 = low-dose ethinylestradiol plus antiandrogenic progestin). In this example, $\beta_3(time*group)_{ij}$ indicates the interaction of

group membership and time predicting VPA (i.e., does the effect of time on VPA vary among the groups?). In this multilevel model, time was still treated as a Level 1 variable and group membership was treated as a Level 2 (or *intra-individual*) variable, as it does not vary within individuals. Rather, group membership reflects differences occurring between participants.

Aim 1, Part 2: To test for differences in lubrication. Initially, a series of paired *t*-tests were conducted to determine whether each group experienced increases in lubrication from pre- to post-film. Next, a multivariate analysis of variance (MANOVA) was used to test for group differences in pre- and post-film levels of lubrication. In the equation, group (low-dose ethinylestradiol plus androgenic progestin, low-dose ethinylestradiol plus antiandrogenic progestin, and control) was entered as the independent variable, and measures of lubrication (pre-film and post-film, separately) were entered as the dependent variables. In a MANOVA, the *F* statistic tests whether the effects (i.e., means of the dependent variables) are equal across the groups. A significant *F* value indicates that there are differences in the means of the dependent variables, but it does not indicate where the differences lie. Thus, in order to isolate the differences while minimizing the number of comparisons (i.e., not running a series of *t*-tests), a Tukey's Honest Significant Difference (HSD) post-hoc test was performed. Tukey's HSD balances the need for conservatism in alpha adjustment with minimizing the risk for Type II errors (Maxwell, 1980). It is considered more conservative than the Least Significant Difference (LSD) test, though less conservative than Scheffe's test (Pizarro, Guerrero, & Galindo, 2002), both of which are common post-hoc procedures.

Aim 2: To examine the mechanistic role of sex hormone binding globulin in the relationship between genital blood flow and lubrication and oral contraceptive use. It was planned that, if significant between-group differences were found on measures of physiological sexual arousal, mediation analyses would be conducted. Using the mediation package for R (Tingley, Yamamoto, Hirose, Keele, & Imai, 2017), serum concentrations of sex hormone binding globulin (SHBG) were examined as a mechanism within the relationship between the study group and physiological sexual arousal response. In each model, group membership was entered as the independent variable, SHBG concentration was entered as the mediating variable, and sexual arousal response (VPA or lubrication) was entered as the dependent variable. Separate models were run for each dependent variable and each between-group comparison (i.e., control versus androgenic, control versus antiandrogenic, and androgenic versus antiandrogenic).

Typical mediation analyses are evaluated based on the relatedness between a series of paths, known as the "a," "b," and "c" paths (Baron & Kenny, 1986). In this model, the "a" path refers to the regression coefficient for the relationship between the independent variable and the mediator, the "b" path refers to the coefficient between the mediator and the dependent variable, and the "c" path refers to the coefficient between the independent and dependent variable through the mediator. R's mediation package, however, does not provide individual path coefficients. Therefore, standardized coefficients for each path were calculated using the QuantPsyc package for quantitative psychology tools (Fletcher, 2012). See Figure 3 for an example path diagram of a standard mediation model.

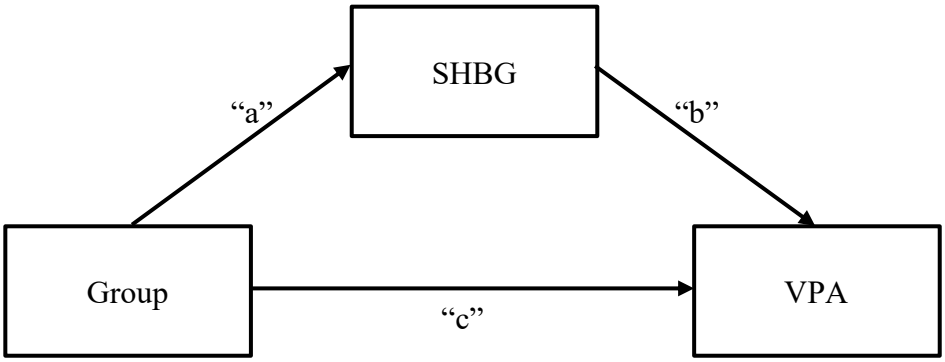

Figure 3. Example mediation model testing sex hormone binding globulin (SHBG) as the mediator between group membership (i.e., androgenic, antiandrogenic, or control) and vaginal pulse amplitude (VPA). In this Figure, the "a" path reflects the direct path from the independent variable to the mediator, the "b" path reflects the direct path from the mediator to the dependent variable, and the "c" path reflects the direct path from the independent variable to the dependent variable. In the case of mediation, an additional path, "c'" reflects the indirect path from the independent variable to the dependent variable via the mediator.

Both average causal and average direct mediation were calculated for each model. The average causal mediation effect (ACME) represents, for example, the expected difference in the potential outcome (e.g., VPA) when the mediator (i.e., SHBG) took the value that would realize under the oral contraceptive pill (OCP) group condition (i.e., one of the OCP groups) as opposed to the control condition (i.e., the non-hormonal control group), while group status itself is held constant. Models used to test the ACME of SHBG on physiological sexual arousal response used the following mediational formula:

$$\delta(t) = E\{Y(t, M(t_1)) - Y(t, M(t_0))\}$$

where t, t_1, t_0 reflect the three values of group membership (low-dose ethinylestradiol plus antiandrogenic progestin, low-dose ethinylestradiol plus androgenic progestin, and control, respectively) such that $t_1 \neq t_0$. M(t) is the potential mediator (i.e., SHBG), and Y (t, M) is

the potential outcome variable (i.e., sexual response). The average direct effect (ADE) of SHBG was calculated as follows:

$$\zeta(t) = E\{Y(t_1, M(t)) - Y(t_0, M(t))\}$$

which represents the expected difference in the outcome when the group that is changed by the mediator is held constant at the value equal to t. These two quantities, the ACME and ADE, were summed to obtain the average total effect of group membership on the outcome, τ. See Tingley et al. (2017) for a thorough explanation of mediation calculation.

Aim 3: To test for differences in measures of subjective sexual arousal among women using oral contraceptive pills with various androgenic properties. Two measures of subjective sexual arousal were examined in the present study: one continuous measure gathered throughout each film presentation, and one discrete measure gathered before and after each film presentation.

Aim 3, Part 1: Continuously measured subjective sexual arousal. Continuously measured subjective sexual arousal was examined in an identical fashion to VPA. Using the nlme package (Pinheiro et al., 2017) for linear and nonlinear mixed effects, growth curve modeling was implemented to examine changes in subjective sexual arousal over time. If significant changes in subjective sexual arousal over time emerged, group membership (i.e., low-dose ethinylestradiol plus androgenic progestin, low-dose ethinylestradiol plus antiandrogenic progestin, and control) was planned to be entered into the equation as a moderator. The equations were identical to those presented above for VPA, except that the subjective sexual arousal variable took the place of the VPA variable.

Aim 3, Part 2: Discretely measured subjective sexual arousal. Similar to the analysis described for the measure of lubrication, a MANOVA was used to test for group differences in discretely measured subjective sexual arousal at the pre- and post-film level. In the equation, group (low-dose ethinylestradiol plus androgenic progestin, low-dose ethinylestradiol plus antiandrogenic progestin, and control) was entered as the independent variable, and measures of subjective sexual arousal (pre-film and post-film) were entered as the dependent variables. As described above, a Tukey's HSD post-hoc test was performed on the resulting MANOVA to isolate the differences while minimizing the number of comparisons.

Aim 4: To test for differences in perceived genital arousal among women using oral contraceptive pills with various androgenic properties. As perceived genital arousal was measured discretely before and after each film presentation, a MANOVA was similarly used to test for group differences in this construct. In the equation, group (low-dose ethinylestradiol plus androgenic progestin, low-dose ethinylestradiol plus antiandrogenic progestin, and control) was entered as the independent variable, and measures of perceived genital arousal (pre- and post-film) were entered as the dependent variables. In agreement with the previous discrete analyses, it was planned that a Tukey's HSD post-hoc test would be performed to locate any differences that emerged.

Aim 5: To explore differences in sexual function among women using oral contraceptive pills with various androgenic properties. Two assessments of sexual function were examined in the present study: one self-report measure and one clinician-administered measure.

Aim 5, Part 1: To explore for differences in self-reported sexual function among women using oral contraceptive pills with various androgenic properties. A MANOVA was used to test for differences in self-reported sexual function among the groups of women. In this equation, group membership (low-dose ethinylestradiol plus androgenic progestin, low-dose ethinylestradiol plus antiandrogenic progestin, and control) was entered as the sole independent variable. Each of the six domains of the Female Sexual Function Index (FSFI; i.e., desire, arousal, lubrication, orgasm, satisfaction, and pain) were entered as dependent variables within the same model. As all domains contribute to the calculation of the FSFI total score, a separate ANOVA was conducted on the total score to reduce redundancy. A Tukey's HSD post-hoc test was planned to locate any significant differences.

Aim 5, Part 2: To explore for differences in clinician-assessed sexual function among women using oral contraceptive pills with various androgenic properties. A series of chi-square tests of independence were conducted to assess for differences in the proportion of decreased genital sensations, as well as the presence of diagnosable female sexual arousal disorder. The chi-square tests of independence were conducted using the MASS package for support functions and datasets for Venables and Ripley's MASS (Ripley et al., 2019). Using the corrplot package for the visualization of correlation matrices (Wei & Simko, 2017), analyses of the residuals were conducted to determine the location of effects that emerged.

4.2.3. Test of Additional Study Measures

Contraceptive side effects. Women in each of the OCP groups were asked to complete a brief survey assessing common contraceptive side effects. Results from this measure were entered into a MANOVA model containing group as the sole independent variable and each possible side effect as the dependent variables. If significance were to emerge, a planned Bonferroni correction for multiple comparisons was to be conducted.

Sexual distress. Results from the FSDS-R produced one variable reflecting the measure's total score. Thus, an ANOVA was used to examine between-group differences in sexual distress. Group membership (low-dose ethinylestradiol plus androgenic progestin, low-dose ethinylestradiol plus antiandrogenic progestin, and control) was entered into the equation as the sole independent variable, and sexual distress total score was entered into the equation as the sole dependent variable.

Vulvovaginal atrophy. The Vulvovaginal Atrophy Assessment contained both dichotomously scored and Likert-style items. Therefore, the dichotomously scored item was assessed with a chi-square test of independence. The chi-square test of independence was conducted using the MASS package for support functions and datasets for Venables and Ripley's MASS (Ripley et al., 2019). The remaining four items were entered into a MANOVA to assess group differences. Similar to the assessment of sexual function, a separate ANOVA was conducted on the measure's total score to reduce redundancy within the MANOVA model.

Positive sexuality. As with the measure of sexual distress, results from the author-constructed assessment the Positive Sexuality Survey produced one variable reflecting the

measure's total score. An ANOVA was therefore used to examine between-group differences in positive sexuality. Group membership was entered into the equation as the sole independent variable, and the measure's total score was entered into the equation as the sole dependent variable.

4.2.4. Statistical Power Considerations

Statistical power is the likelihood of rejecting the null hypothesis (e.g., determining that there are significant group differences) when the null hypothesis is false (e.g., when there truly are significant group differences). Repeated measures designs are virtually always more powerful than designs in which measurements are only collected at one time (Murphy, Myors, & Wolach, 2014) as the increase in time points allows for increased reliability of the data. Given the sheer quantity of time points gathered through the time-series data collection methods in the present study, these equations are likely the most powerful of the conducted analyses. Therefore, growth curve modeling analyses were not considered when calculating statistical power.

A power analysis for a multivariate ANOVA with three groups and a low ($r = 0.25$) correlation between time points indicated that a total sample of $N = 123$ would be required. This would allow for 90% power to detect a true effect with an α of 0.05 (two-tailed) and a small effect ($f = .2$). The a priori effect size of .2 was selected as a conservative effort; smaller effect sizes require a larger sample size to be detected, whereas larger effect sizes require a smaller sample size. Thus, with a final sample size of 130 women, the study as a whole was sufficiently powered to detect a true small effect.

4.2.5. Procedure for Missing Data

For between-group comparisons, participants with data missing from only the measures in question were excluded. For example, if a participant was missing data on perceived genital arousal, her data were excluded from the model involving perceived genital arousal only, but not the other models for which she did have present and viable data. The computer system for self-report data required women to select an answer for every item, even if they selected "Skip," therefore minimal data were missing in this study.

CHAPTER 5: RESULTS

5.1. FINDINGS OF THE MAJOR STUDY HYPOTHESES

5.1.1. Validity Check for Order Effects of Video Manipulation

Women were randomly assigned to the order in which their physiological sexual arousal was measured (i.e., blood flow followed by lubrication, or lubrication followed by blood flow). As such, assessments of potential order effects were conducted. Linear mixed effects models including sexual arousal measurement as the dependent variable and measurement order as the independent variable found no significant order effects for women's vaginal pulse amplitude (VPA), $t(125) = 0.388$, $p = .698$, nor subjective sexual arousal, $t(125) = 0.617$, $p = .538$, responses. Results from a multivariate analysis of variance (MANOVA) found no differences in the order in which lubrication was measured, $F(1, 127) = 1.911$, $p = .152$.

Similarly, subjective sexual arousal and perceived genital arousal were measured in response to both sexual films. Thus, to assess for possible carry-over effects, differences on these measures between the two films were assessed. No significant differences on pre- nor post-film levels of perceived genital arousal, $t(129) = 0.989$, $p = .201$ and $t(129) = -1.308$, $p = .193$, respectively, and perceived autonomic arousal, $t(129) = 0.895$, $p = .371$ and $t(129) = 0.478$, $p = .633$, respectively, were found between the two films. These results suggest there was no measured effect of the first film on physiological and self-report measures gathered during the second film. Given this lack of differences, measurement order was not controlled for in subsequent analyses containing any of these variables.

5.1.2. Group Variations in Vaginal Blood Flow

Significant increases in VPA over the course of the sexual films were depicted in all three groups of women. In line with the study hypothesis, naturally-cycling women exhibited the strongest VPA response (b_0 = 26.01 millivolts; mV), with a notably greater baseline level of VPA compared to the two groups of women taking oral contraceptive pills (OCPs). This was followed by women taking androgenic OCPs (b_0 = 20.80 mV) and then women taking antiandrogenic OCPs (b_0 = 14.67 mV), who displayed the weakest VPA response. See Figure 4 for a visualization of the VPA responses for each group.

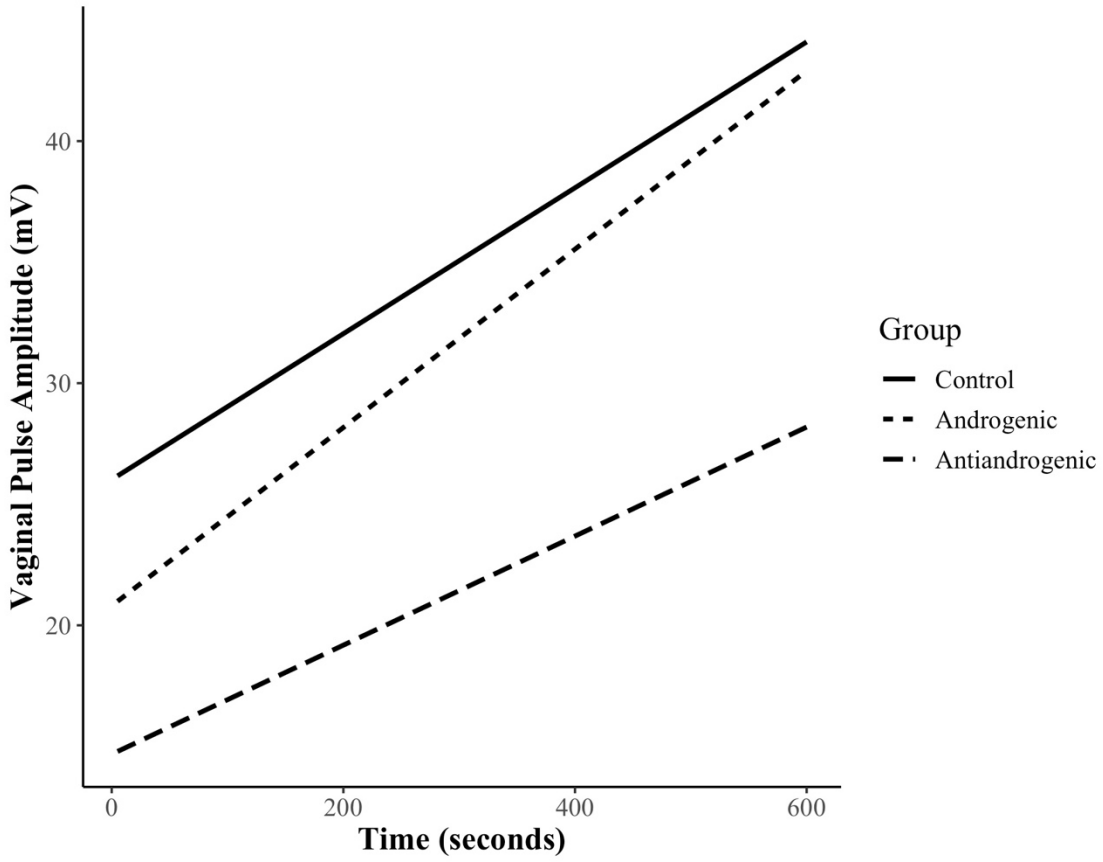

Figure 4. Linear slopes indicating average change in vaginal blood flow over the course of an erotic film for women in the control, androgenic, and antiandrogenic groups. In this Figure, vaginal pulse amplitude is

measured in millivolts, indicated as "mV." Women in the control group (i.e., not taking oral contraceptive pills) exhibited a significantly greater response than did women in androgenic or antiandrogenic group. For clarity, this Figure displays unstandardized effects.

As can be seen in Figure 4, women taking androgenic OCPs also displayed the steepest slope in VPA, with an average increase of 0.036 mV/5 seconds, which equates to 0.432 mV/minute, $t(5830) = 44.33$, $p < .001$. This effect was followed by women in the control group, who had an average increase of 0.030 mV/5 seconds, or 0.36 mV/minute, $t(6782) = 34.01$, $p < .001$. Lastly, in addition to exhibiting the weakest overall VPA response, women taking antiandrogenic OCPs also displayed the flattest slope, with an average increase of 0.022 mV/5 seconds, or 0.264 mV/minute, $t(2498) = 29.24$, $p < .001$.

A moderated hierarchical linear regression found significant effects of study group on the slope of the VPA line for women in the androgenic and antiandrogenic groups. As the temporal nature of VPA would indicate, this effect was only significant when examining change in VPA over time; estimates that did not include time within the model were not significant. This suggests that the VPA responses for women in both of these groups were significantly different from, and, in this case, significantly lower than, the responses of women in the control group. This effect was most pronounced in women taking antiandrogenic OCPs. These results suggest the presence of a slight inhibitory effect of androgenic OCPs and a marked inhibitory effect of antiandrogenic OCPs on vaginal blood flow, confirming this study's primary hypothesis. Refer to Table 5 for the complete model output.

Table 5.

Moderated Hierarchical Regression Estimates for Vaginal Pulse Amplitude as Predicted by Time (Level 1) and Oral Contraceptive Pill Group (Level 2)

Variable	Value	*SE*	*df*	*t*	*p*
Intercept	26.018	3.102	15110	8.387	.0000
Time	0.030	0.001	15110	38.355	.0000
Androgenic	-5.212	4.562	124	-1.142	.2554
Antiandrogenic	-11.343	5.978	124	-1.897	.0601
Time x Androgenic	0.006	0.001	15110	5.792	.0000
Time x Antiandrogenic	-0.007	0.001	15110	-5.025	.0000

Note: SE = standard error; *df* = degrees of freedom. Estimates for each Level 2 analysis reflect results for the stated group against the control group. Women in the control group exhibited significantly greater vaginal pulse amplitude responses than did women in either of the oral contraceptive pill groups.

5.1.3. Group Variations in Vaginal Lubrication

Significant increases in vaginal lubrication from pre- to post-film were demonstrated in each of the three study groups. On average, women in the non-hormonal control group experienced a 5.28 mm ($SD = 5.63$) increase in lubrication from pre- to post-film, $t(58) = 7.185$, $p < .0001$. Women taking androgenic OCPs exhibited a lesser lubrication response, with an average increase of 3.89 mm ($SD = 4.07$) of lubrication, $t(49) = 6.754$, $p < .0001$). Finally, women taking antiandrogenic OCPs exhibited an average increase of 4.16 mm ($SD = 3.03$) of vaginal lubrication, $t(20) = 6.292$, $p = .000003$). Results of a MANOVA identified significant differences in lubrication scores among the three

groups of women, $F(2, 254) = 2.254$, $p = .063$. See Figure 5 for a visualization of pre- and post-film levels of lubrication for the three study groups.

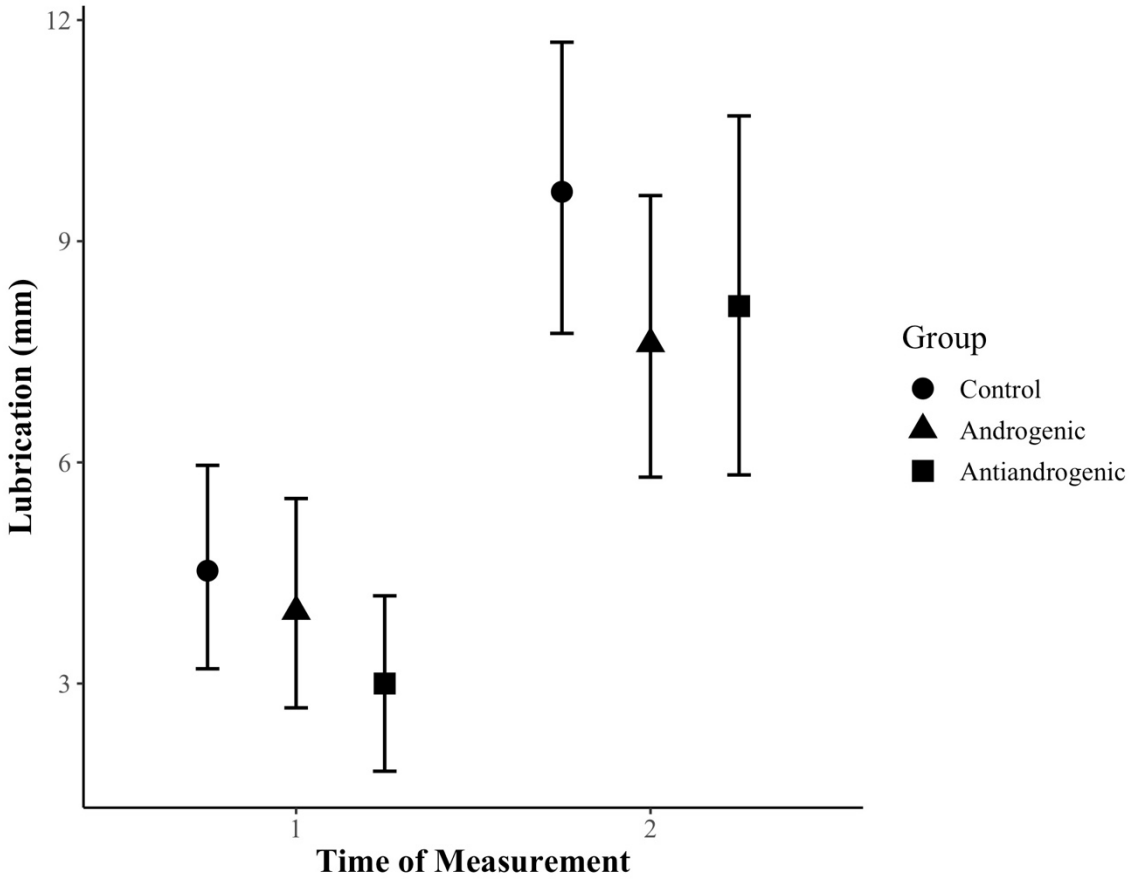

Figure 5. Average pre- and post-film measures of lubrication for women in the control, androgenic, and antiandrogenic groups. In this Figure, lubrication is measured in millimeters, indicated as "mm." Pre-film measures are indicated as Time "1," and post-film measures are indicated as Time "2." Error bars represent upper and lower percentiles. Women taking antiandrogenic oral contraceptive pills exhibited significantly weaker baseline lubrication compared to women in the other two groups, whereas those in the control group exhibited a significantly stronger lubrication response post-film compared to women in the other two groups.

In the event that significant differences were to emerge, it was planned that Tukey's Honest Significant Difference post-hoc analyses would be conducted to identify the

location(s) of the significant effect(s). These post-hoc analyses revealed significantly lower levels of baseline (i.e., pre-film, unaroused) lubrication in women taking antiandrogenic OCPs compared to women in the control group ($p = .060$), as well as significantly lower levels of post-film lubrication (i.e., aroused) in women taking androgenic ($p = .064$) and antiandrogenic ($p = .045$) OCPs compared to those in the control group. These results mimic the previously reported variations in VPA, suggesting that type of OCP influences physiological sexual arousal in women. This appears to be particularly true for antiandrogenic OCPs.

5.1.4. Mediating Effect of Sex Hormone Binding Globulin

Prior to examining the potential mediating effect of sex hormone binding globulin (SHBG) on physiological sexual arousal, between-group differences were assessed. Had no between-group differences emerged, mediation would not be conducted. The study's design of random sampling for participation in the blood draw yielded 87 total samples: 37 from women in the control group, 35 from women in the androgenic group, and 15 from women in the antiandrogenic group. Results from an ANOVA indicated significant differences in serum SHBG concentrations across the three study groups, $F(2) = 85.50$, $p < .0001$. Planned post-hoc analyses conducted to identify the location(s) of the significant difference(s) found all three comparisons to be significant (i.e., control versus androgenic, control versus antiandrogenic, and androgenic versus control; ps $< .0001$). As expected, serum SHBG concentrations were lowest in women in the control group ($M = 54.76$, $SD = 26.19$), followed by the androgenic group ($M = 109.99$, $SD = 45.82$), and finally the antiandrogenic group ($M = 253.01$, $SD = 88.64$). See Figure 6 for plotted results.

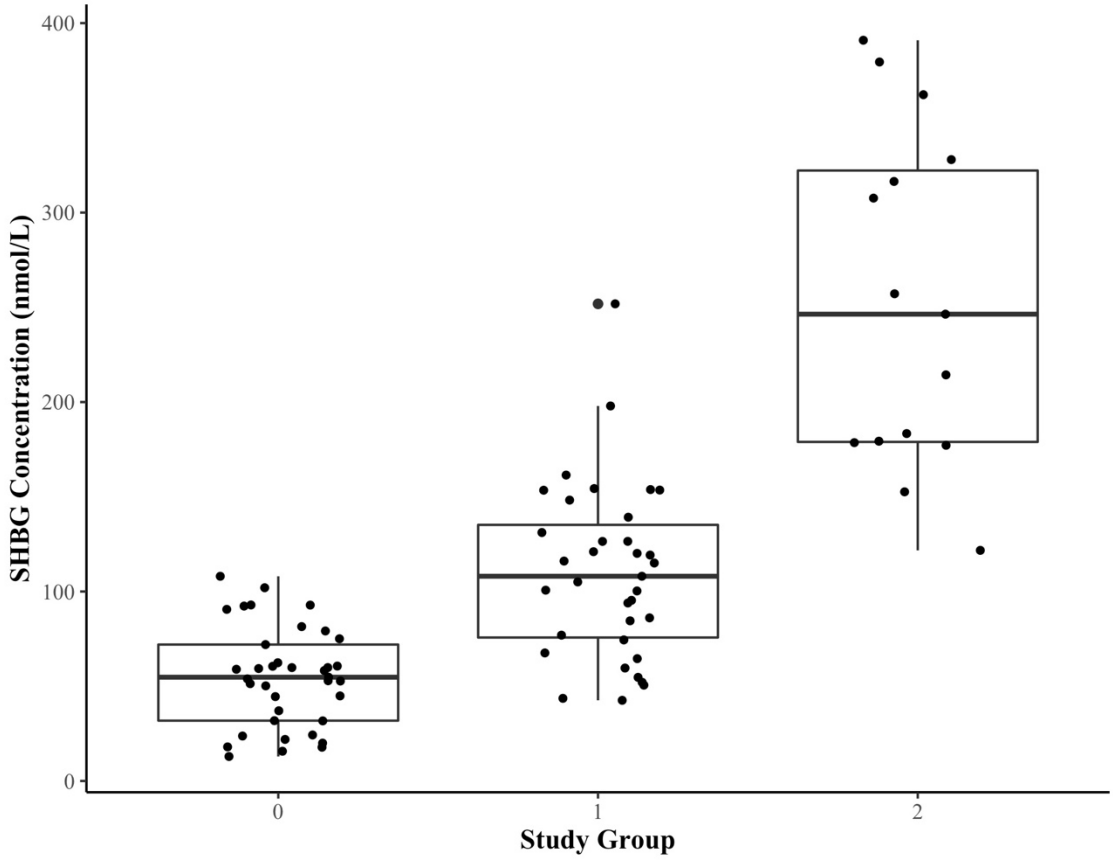

Figure 6. Average and actual serum sex hormone binding globulin ("SHBG") levels for women in each group. Here, SHBG is measured in nanomoles per liter (nmol/L). Control, androgenic, and antiandrogenic groups are noted as 0, 1, and 2, respectively, with significant between-group differences for each comparison.

5.2.4.1. Findings for Vaginal Blood Flow

The relationship between OCP group and VPA was partially, but not meaningfully, mediated by the serum concentrations of SHBG. As Figure 7 illustrates, for women taking androgenic OCPs compared to women in the control group, the standardized regression coefficient between study group and SHBG was statistically significant, with an average direct effect (ADE) of .640, $p < .0001$. The standardized regression coefficient between

SHBG and VPA was also significant, ADE = -.054, $p < .0001$, as was the indirect effect of study group on VPA, $r = -.086$, $p < .0001$, indicating a related series of effects.

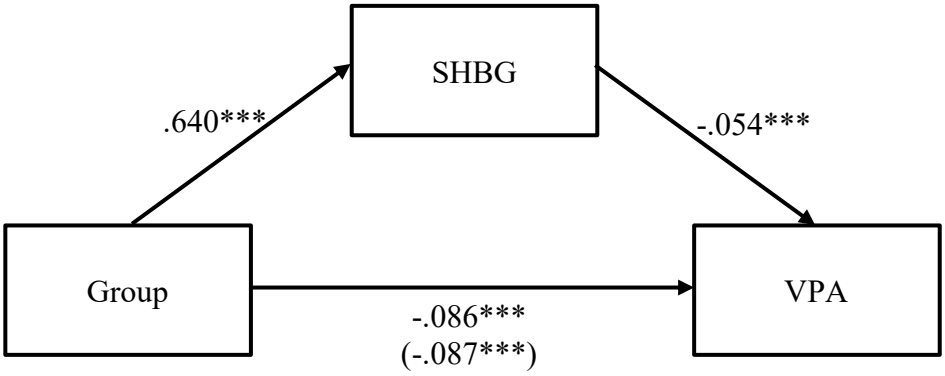

Figure 7. Model reflecting the effect of study group on vaginal pulse amplitude (VPA), as mediated by sex hormone binding globulin (SHBG) for women in the androgenic and control groups. Significant direct and indirect effects indicate that group influences SHBG, which, in turn, influences VPA, though this series of effects was not significant through mediation.

The significance of the entire model was tested using quasi-Bayesian procedures. Unstandardized indirect effects were computed for 1,000 simulated samples; the 95% confidence interval was computed by determining the indirect effects at the 2.5th and 97.5th percentiles. The simulated unstandardized indirect effect was -3.924 and the 95% confidence interval ranged from -4.922 to -2.89 and was statistically significant, $p < .0001$. Further investigation of the model revealed that this was driven by the direct effect of study group on VPA; the product of the a and b paths was not significant. The average causal mediation effect (ACME) was also not significant (ACME = 0.054 [-0.746, 0.870], $p = .900$), with a proportional mediation of -0.01.

A similar pattern emerged for women taking antiandrogenic OCPs compared to women in the control group. In this model, the standardized regression coefficient for the

path between group and SHBG was statistically significant, ADE = .873, $p < .0001$, as was the standardized coefficient for the path between SHBG and VPA, ADE = -.277, $p < .0001$. The indirect effect of study group on VPA was also significant, $r = -.310$, $p < .0001$. The simulated unstandardized indirect effect was -15.765, and the 95% confidence interval ranged from -16.965 to -14.550 and was statistically significant, $p < .0001$. Investigation of the model revealed that this was similarly driven by the direct effect of group on VPA; the product of the a and b paths was not significant (ACME = -1.133 [-3.225, 1.130], $p = .290$), with a proportional mediation of 0.07. See Figure 8 for a path model of these effects.

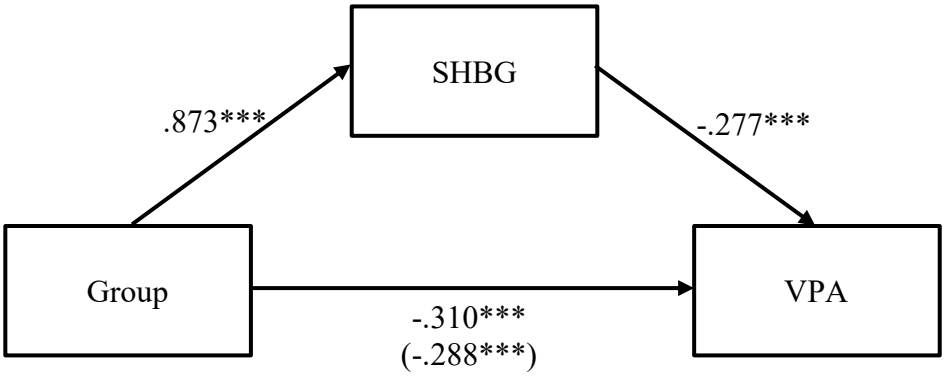

Figure 8. Model reflecting the effect of study group on vaginal pulse amplitude (VPA), as mediated by sex hormone binding globulin (SHBG) for women in the antiandrogenic and control groups. Significant direct and indirect effects indicate that group influences SHBG, which, in turn, influences VPA, though this series of effects was not significant through mediation.

Finally, as indicated in Figure 9, partial, but not meaningful, mediation occurred when comparing women taking androgenic OCPs against women taking antiandrogenic OCPs. Similar to the other two models, significant effects emerged for the direct path between study group on SHBG (ADE = .734, $p < .0001$), the direct path between SHBG and VPA (ADE = -.196, $p < .0001$), and the indirect path between study group and VPA (*r*

= -262, $p < .0001$). The simulated unstandardized indirect effect was -11.764, and the 95% confidence interval ranged from -12.845 to -10.700 and was statistically significant, $p < .0001$. The product of the a and b paths was not significant (ACME = -0.241 [-1.370, 0.097], $p = .068$) and had a proportional mediation of 0.02; the significance of the model was again driven by the indirect effect. Taken together, this series of results indicate that differences in SHBG concentration influence, but do not fully explain, the observed between-group differences in VPA.

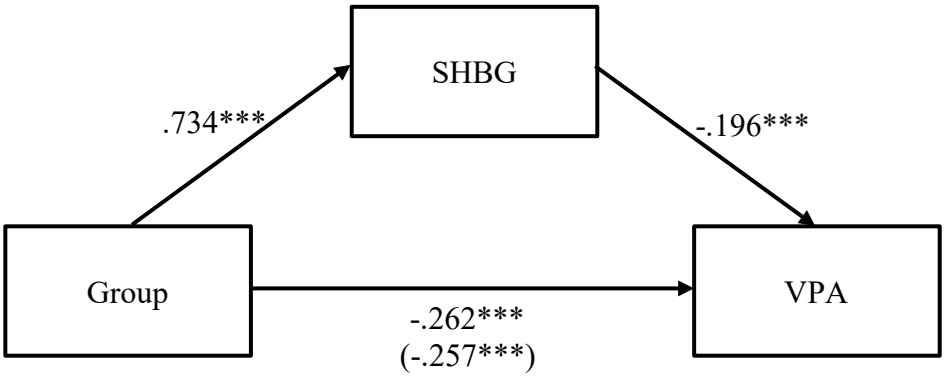

Figure 9. Model reflecting the effect of study group on vaginal pulse amplitude (VPA), as mediated by sex hormone binding globulin (SHBG) for women in the androgenic and antiandrogenic groups. Significant direct and indirect effects indicate that group influences SHBG, which, in turn, influences VPA, though this series of effects was not significant through mediation.

5.2.4.2. Findings for Vaginal Lubrication

Post-film measures of lubrication were used in the following mediation models. This was selected as opposed to pre-film measures or difference scores (i.e., change from pre- to post-film). As women's pre- and post-film measures of lubrication differed, variations in lubrication difference scores may have been masked during analyses. For example, the difference scores between a participant with below-average measures of both

pre- and post-film lubrication and one with above-average levels may not appear different from each other, despite the first participant achieving a lower overall level of lubrication. This lower level of overall lubrication may be clinically meaningful and should not be overlooked. Thus, post-film measures of lubrication were selected as the index of choice for the subsequent analyses in hopes of capturing meaningful between-group differences.

As depicted in Figure 10, no significant mediation occurred in women taking androgenic OCPs compared to women in the control group. There was a significant direct effect of group on SHBG, ADE = .602, $p < .0001$, though the effect of SHBG on lubrication was not significant, ADE = -.188, $p = .113$. The indirect effect of group on lubrication was significant, however, so the mediation model was continued, $r = -.289$, $p = .014$. Using quasi-Bayesian procedures, the significance of the model was estimated through the computation of 1,000 simulated samples. The simulated unstandardized indirect effect was -3.8377, and the 95% confidence interval ranged from -7.007 to -0.61 and was statistically significant, $p = 0.018$. The causal mediation, however, was not, ACME = -0.172 [-2.5479, 2.100], $p = 0.898$, and the model had a proportional mediation of .03.

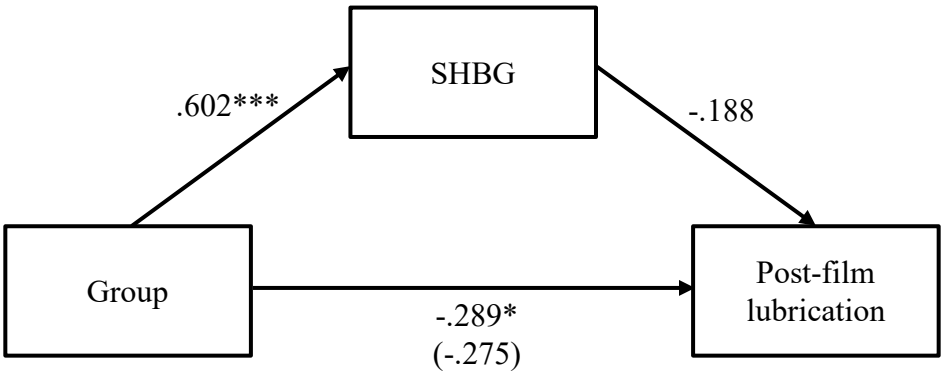

Figure 10. Model reflecting the effect of study group on post-film levels of lubrication, as mediated by sex hormone binding globulin (SHBG) for women in the androgenic and control groups. The significant direct

between group and SHBG indicates that SHBG varied significantly across group, and the significant indirect effect from group to post-film lubrication suggests indicates that lubrication also varied significantly across group. The role of SHBG in this indirect relationship, however, does not appear to be sufficient for mediation.

Similar patterns were found for women taking antiandrogenic OCPs compared to women in the control group. In this model, the standardized regression coefficient for the direct path between study group and SHBG was statistically significant, ADE = .870, $p <$ .0001, though the standardized coefficient for the direct path between SHBG and lubrication was not significant, ADE = -0.175, p = .213. There was a significant indirect effect of group on lubrication, r = -.268, p = .054. The simulated unstandardized total effect was -3.947 with a 95% confidence interval that ranged from -7.945 to -0.03 and was statistically significant, p = 0.050. However, the causal mediation depicted by the model indicated no significant mediation effects of SHBG on the relationship between study group and lubrication, ACME = 2.818 [-3.850, 10.130], p = 0.444. Proportional mediation for this model was -.70. See Figure 11 for a path diagram highlighting these results.

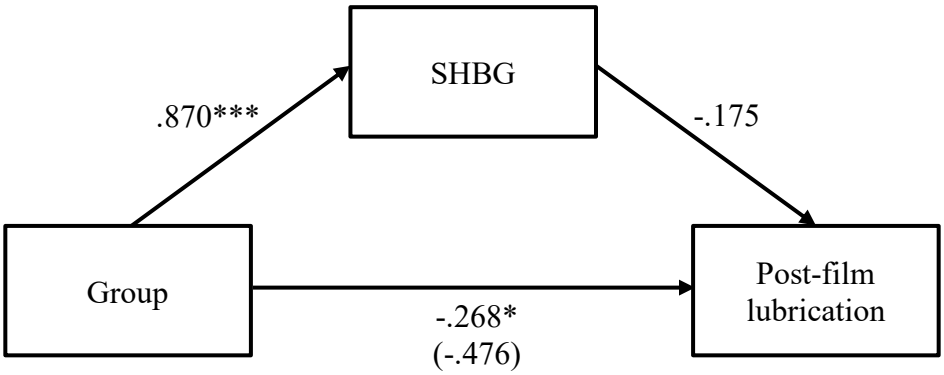

Figure 11. Model reflecting the effect of study group on post-film levels of lubrication, as mediated by sex hormone binding globulin (SHBG) for women in the antiandrogenic and control groups. The significant direct between group and SHBG indicates that SHBG varied significantly across group, and the significant

indirect effect from group to post-film lubrication suggests indicates that lubrication also varied significantly across group. The role of SHBG in this indirect relationship, however, does not appear to be sufficient for mediation.

A slightly different pattern of results emerged for women in the androgenic compared to antiandrogenic groups. For these women, there was a significant direct effect of study group on SHBG, ADE = 0.736, $p < .0001$, and no significant direct effect of SHBG on post-film levels of lubrication, ADE = 0.025, $p = .859$. However, the indirect effect of group on lubrication was also nonsignificant, with an r of -.008, $p = .954$. The simulated model confirmed these results, indicating a total effect of -0.087, with a 95% confidence interval that ranged from -3.427 to 3.35 $p = 0.96$. Similarly, the causal mediation was also nonsignificant, ACME = 0.521 [-2.903, 4.35], $p = 0.81$. Proportional mediation for this model was -.04. See Figure 12. Taken together, this series of results indicate that, whereas SHBG concentration varies by women's hormonal profile, it may not play a large enough role in variations in lubrication to be evident within a mediation model of this nature.

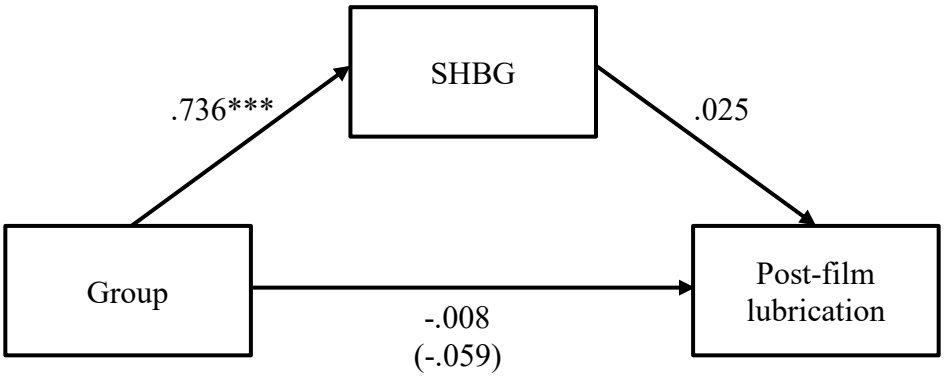

Figure 12. Model reflecting the effect of study group on post-film levels of lubrication, as mediated by sex hormone binding globulin (SHBG) for women in the androgenic and antiandrogenic groups. The only significant path that emerged within this model was the direct path from study group to SHBG, indicating that SHBG levels varied significantly by group, but this does not appear to play a role in post-film lubrication.

5.1.5. Group Variations in Subjective Sexual Arousal

5.1.5.1. Findings for Continuous Subjective Sexual Arousal

As no significant differences were found between subjective sexual arousal measured during the first and second film sessions for either group, for simplicity, only subjective sexual arousal responses that were captured during the first film were included in the following analyses. Significant increases in subjective sexual arousal over the course of the films were depicted in all three groups of women. Women in the control group exhibited the flattest slope and, ultimately, achieved the lowest level of subjective sexual arousal at the end of the film. They displayed an average increase of 0.00104 units/5 seconds, which equates to 0.012 units/minute, $t(6782) = 87.88$, $p < .001$.

On the other hand, women in the androgenic and antiandrogenic groups exhibited remarkably similar slopes for their subjective sexual arousal responses. For both groups of women taking OCPs, subjective sexual arousal responses were significantly greater than those of women in the control group. Women in these two groups also exhibited steeper slopes of their subjective sexual arousal lines, which reflects more rapid change in this measure. Women in the androgenic group experienced an average increase of 0.001 mV/5 seconds, or 0.014 mV/minute, $t(5830) = 88.96$, $p < .001$, and women taking antiandrogenic OCPs displayed an average increase of 0.00128 mV/5 seconds, which translates to increases of 0.015 mV/minute, $t(2498) = 61.65$, $p < .001$. See Figure 13 for a graphical depiction of the subjective sexual arousal slopes for each study group.

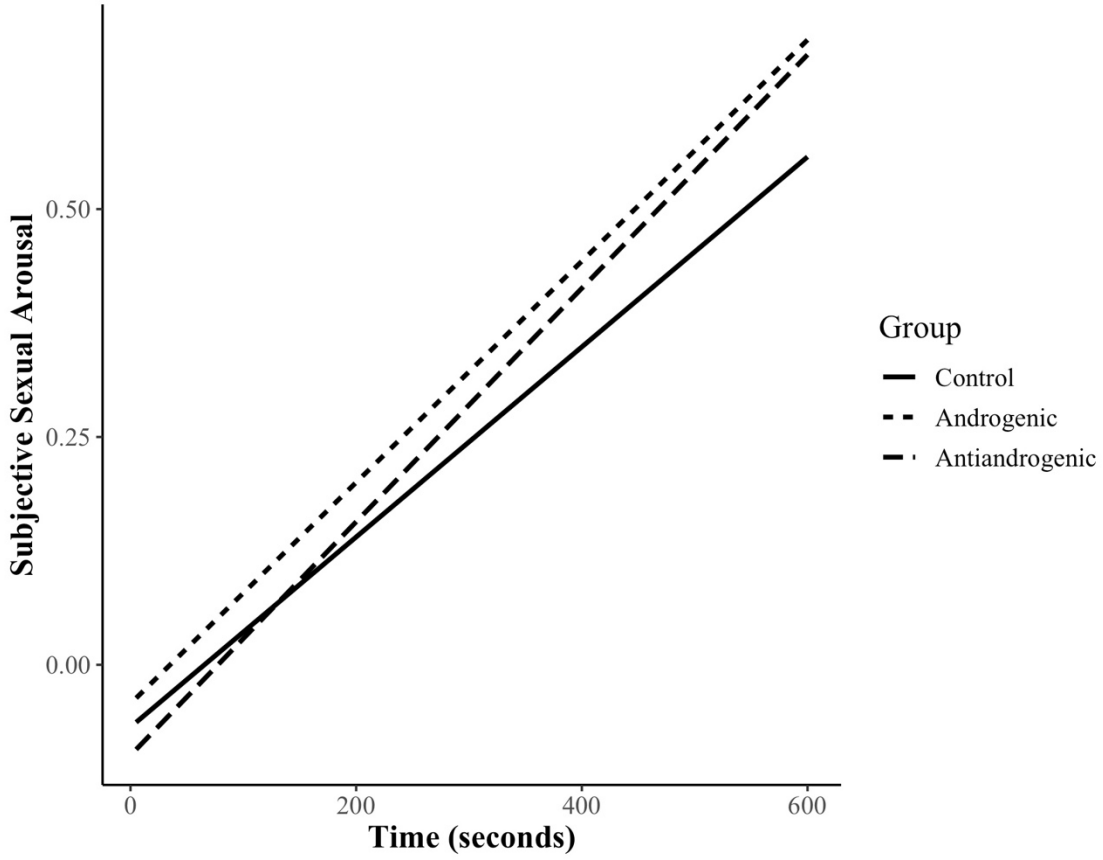

Figure 13. Linear slopes indicating average change in subjective sexual arousal over the course of an erotic film for women in the control, androgenic, and antiandrogenic groups. Women in the androgenic and antiandrogenic groups exhibited significantly greater subjective sexual arousal responses compared to women in the control group. For ease of interpretation, this Figure depicts unstandardized modeled effects.

A moderated hierarchical linear regression found significant effects of the study group on the slope of the subjective sexual arousal line over time for both of the OCP groups. According to this model, there were significantly greater subjective sexual arousal responses in women taking androgenic and antiandrogenic OCPs compared to women in the control group. Women in the control group displayed the lowest level of subjective sexual arousal throughout the film. In contrast to the study's hypothesis, these results

suggest a possible enhancing effect of OCPs on women's experience of subjective sexual arousal in response to erotic stimuli. See Table 6 for the complete model output.

Table 6.

Moderated Hierarchical Regression Estimates for Subjective Sexual Arousal as Predicted by Time (Level 1) and Oral Contraceptive Pill Group (Level 2)

Variable	Value	*SE*	*df*	*t*	*p*
Intercept	-0.068	0.025	15110	-2.725	.006
Time	0.001	0.00001	15110	84.800	.0001
Androgenic	0.025	0.036	124	0.698	.486
Antiandrogenic	-0.031	0.048	124	-0.641	.522
Time x Androgenic	0.0001	0.00001	15110	9.445	.0001
Time x Antiandrogenic	0.0002	0.00002	15110	10.056	.0001

Note: SE = standard error; *df* = degrees of freedom. Estimates for each Level 2 analysis reflect results for the stated group against the control group. Women in the androgenic and antiandrogenic oral contraceptive pill groups exhibited significantly greater degrees of subjective sexual arousal than did women in the control group.

5.1.5.2. Findings for Discrete Subjective Sexual Arousal

As no significant differences were found between subjective sexual arousal measured with respect to the first and second film sessions, only subjective sexual arousal data for the first film were used in the following analyses. A MANOVA examining differences in pre- and post-film levels of discretely measured subjective sexual arousal among the three study groups revealed no significant differences, $F(2, 254) = 1.075$, $p =$

.369. On average, scores for women in the control group increased from 5.64 (*SD* = 2.31) to 9.11 (*SD* = 2.95). Scores for women in the androgenic group similarly increased from 5.28 (*SD* = 2.26) to 8.98 (*SD* = 2.66), and, similarly, those for women in the antiandrogenic group increased from 4.61 (*SD* = 1.88) to 9.47 (*SD* = 2.15). These results suggest that any between-group differences in subjective sexual arousal are best detected when examining continuous changes in this construct throughout stimulus exposure; it appears as though it is important to take into consideration the temporal nature of subjective sexual arousal when comparing responses from these groups of women. See Tables 7 and 8 for pre- and post-film scores of each item comprising this measure.

Table 7.

Item-Level Analyses for Pre-Film Mental Sexual Arousal Across the Study Groups

	Control ***N* = 59**		**Androgenic** ***N* = 50**		**Antiandrogenic** ***N* = 21**	
Arousal item	***M***	***SD***	***M***	***SD***	***M***	***SD***
Sexually aroused	1.42	0.79	1.30	0.70	1.14	0.65
Mental sexual arousal	1.44	0.85	1.50	0.90	1.14	0.35
Sexually turned off	2.77	2.15	2.48	1.96	2.33	1.65

Note: M = mean; *SD* = standard deviation. Scores for the item "Sexually turned off" have been reverse scored. No significant between-group differences were identified.

Table 8.

Item-Level Analyses for Post-Film Mental Sexual Arousal Across the Study Groups

	Control ***N*** **= 59**		**Androgenic** ***N*** **= 50**		**Antiandrogenic** ***N*** **= 21**	
Arousal item	***M***	***SD***	***M***	***SD***	***M***	***SD***
Sexually aroused	3.84	1.66	3.78	1.21	4.09	1.37
Mental sexual arousal	3.55	1.71	3.74	1.42	3.85	1.45
Sexually turned off	1.71	1.26	1.46	0.70	1.52	0.81

Note: M = mean; *SD* = standard deviation. Scores for the item "Sexually turned off" have been reverse scored. No significant between-group differences were identified.

5.1.6. Group Variations in Perceived Genital Arousal

Ratings of perceived genital arousal were not significantly different between the first and second films; therefore, all reported results reflect ratings gathered in relation to the first film session. A MANOVA model revealed no significant between-group differences on pre-film levels of perceived genital arousal, $F(2, 246) = 0.606$, $p = .836$. This lack of difference was expected and likely due to a general floor effect. In other words, pre-film measures of this construct were expected be minimal as arousal had yet to be induced, thus there were minimal to no genital arousal sensations to be perceived. Significant increases on this domain were noted for each group, however, with *t*s ranging from |7.898| to |9.428|. These values indicate relatively large changes in perceived genital arousal from pre- to post-film for each study group. See Table 9 for pre-film item-level raw scores for each study group.

Table 9.

Item-Level Analyses for Pre-Film Genital Arousal Across the Study Groups

	Control ***N* = 59**		**Androgenic** ***N* = 50**		**Antiandrogenic** ***N* = 21**	
Arousal item	***M***	***SD***	***M***	***SD***	***M***	***SD***
Warmth	1.96	1.12	1.72	1.03	1.47	0.60
Wetness/lubrication	1.88	1.06	1.82	1.06	1.57	0.59
Pulsing/throbbing	1.16	0.62	1.16	0.42	1.23	0.53
Tenseness/tightness	1.55	1.00	1.48	0.93	1.47	0.98
Any genital feeling	1.88	1.05	1.88	0.93	1.71	0.84
Total score	8.45	3.87	8.06	3.47	7.47	2.56

Note: M = mean; *SD* = standard deviation. To avoid redundancy, the total score of this subscale was not included in the MANOVA model. No significant between-group differences were identified.

Despite the significant increases from pre- to post-film for each study group, no significant between-group differences were found for post-film ratings of perceived genital arousal, $F(2, 246) = 0.823$, $p = .626$. Contrary to the study hypothesis that ratings of perceived genital arousal would mimic the observed patterns of physiological measures of arousal, no hormone-related variations were detected. Indeed, these results suggest that OCP use does not appear to influence women's perceptions of their genital sexual arousal, despite the presence of physiological deficits. See Table 10 for post-film item-level raw scores for each study group.

Table 10.

Item-Level Analyses for Post-Film Genital Arousal Across the Study Groups

	Control *N* = 59		Androgenic *N* = 50		Antiandrogenic *N* = 21	
Arousal variable	***M***	***SD***	***M***	***SD***	***M***	***SD***
Warmth	3.27	1.41	3.36	1.54	3.28	1.48
Wetness/lubrication	3.77	1.56	3.74	1.29	3.61	1.43
Pulsing/throbbing	2.89	1.79	3.22	1.65	3.00	1.76
Tenseness/tightness	2.49	1.47	2.82	1.58	2.76	1.81
Any genital feeling	3.91	1.50	4.04	1.51	4.23	1.54
Total score	16.35	6.45	17.18	6.17	16.90	6.70

Note: M = mean; *SD* = standard deviation. To avoid redundancy, the total score of this subscale was not included in the MANOVA model. No significant between-group differences were identified for this measure.

5.1.7. Group Variations in Sexual Function

5.1.7.1. Self-Reported Sexual Function

Results from a MANOVA indicated no significant between-group differences emerged for any domain of sexual functioning, $F(2, 246) = 1.501$, $p = .123$. An ANOVA confirmed there were no significant differences in overall sexual function, $F(2) = 0.369$, $p = .692$. On average, women's total score on the Female Sexual Function Index (FSFI) was 27.00 (SD = 5.88), which is slightly greater than the cutoff (26.55) score for sexual dysfunction (Wiegel et al., 2005). Though this indicates a relatively low level of sexual function for women who do not have sexual dysfunction, such scores are not abnormal for

women of this age (Meyer-Bahlburg & Dolezal, 2007), and are driven, in part, by lower scores on the Orgasm domain. In the present study, scores on the Orgasm domain were nearly one point lower than scores on the other domains (3.74 versus 4.65, respectively). See Table 11 for group-level domain and total scores for the FSFI.

Table 11.

Female Sexual Function Index Domain and Total Scores for Each Study Group

	Control ***N* = 59**		**Androgenic** ***N* = 50**		**Antiandrogenic** ***N* = 21**	
FSFI Domain	***M***	***SD***	***M***	***SD***	***M***	***SD***
Desire	4.14	0.89	4.33	0.91	4.11	0.83
Arousal	4.73	1.11	4.65	1.21	4.88	0.88
Lubrication	4.93	1.41	5.03	1.21	4.71	1.06
Orgasm	3.74	1.74	3.59	1.69	4.13	1.18
Satisfaction	4.51	1.62	4.34	1.45	5.12	0.86
Pain	4.87	1.66	4.67	1.41	4.97	1.39
Total score	26.99	6.63	26.62	5.74	27.94	3.64

Note: FSFI = Female Sexual Function Index; *M* = mean; *SD* = standard deviation. No significant between-group differences emerged on any of the six domains of sexual function nor overall sexual function (as depicted by the measure's total score).

5.1.7.2. Clinician-Assessed Sexual Function

In contrast to self-reported sexual function, notable between-group differences in sexual arousal function emerged during the clinical interview. Female sexual arousal disorder was identified in seven (33.33%) of women taking antiandrogenic OCPs, 12

(24.00%) of women taking androgenic OCPs, and five (8.47%) of women in the control group. As later described, these results were driven, primarily, by decrements in vaginal lubrication. A chi-square test of independence indicated a significant relationship between study group and the presence of female sexual arousal disorder, $\chi^2(2) = 8.013$, $p = .018$. An analysis of the residuals of the chi-square test indicated that women in the antiandrogenic group were significantly more likely, and those in the control group were significantly less likely, to meet the criteria for female sexual arousal disorder. Despite the increased prevalence in women taking androgenic OCPs compared to women in the control group (i.e., 24.00% versus 8.47%), this difference did not reach statistical significance.

As a part of the clinical interview for female sexual arousal disorder, changes in (i.e., increases, no changes, decreases, or absence of) five prominent components of genital sexual arousal were assessed. Whereas no differences were found for pleasurable sexual feelings, pulsing/throbbing, fullness/pressure/engorgement, and genital warmth, women in the antiandrogenic group more often reported decreased or absent experiences of genital lubrication compared to women in the control group. A similar pattern emerged for women in the androgenic group, though this difference was not significant; rates of decreased or absent lubrication were twice as high for women in the antiandrogenic compared to the androgenic group. It, therefore, appears as though women taking antiandrogenic OCPs are most impacted by female sexual arousal disorder compared to women taking androgenic OCPs or those who are naturally-cycling. Refer to Table 12 for summary statistics of the frequency with which women in each group endorsed decrements in the five sexual arousal sensations used to screen for female sexual arousal disorder.

Table 12.

Number of Women Reporting Decreased or Absent Sexual Arousal Sensations by Group

	Control *N* = 59		Androgenic *N* = 50		Antiandrogenic *N* = 21		
Genital sensation	***n***	**%**	***n***	**%**	***n***	**%**	χ^2
Pleasurable sexual feelings	5	8.47	9	18.00	4	19.04	2.626
Pulsing or throbbing	13	26.00	6	14.63	5	33.33	3.755
Fullness, pressure, or engorgement	6	20.68	8	26.66	2	16.66	0.586
Warmth	5	10.41	2	5.26	4	2.83	7.737
Wetness or lubrication	5	8.47	14	28.57	13	61.90	24.555***

Note: A significantly greater frequency of women taking antiandrogenic oral contraceptive pulls reported decreased or absent lubrication compared to women in the control group. A significantly greater proportion of women in the antiandrogenic group reported decreased or absent vaginal wetness or lubrication compared to women in either of the other two groups.

*** $p = .00006$

5.2. Additional Study Measures

5.2.1. Contraceptive Side Effects

Women in the control group (i.e., not using OCPs) were excluded from this analysis. Two reduce redundancy of testing and likelihood of detecting false positives, all 25 assessed contraceptive side effects were entered into the same MANOVA model. Results from this model indicated no significant differences between the two OCP groups on any item, $F(1, 25) = 1.394$, $p = .163$. The most common side effects reported by women taking androgenic OCPs included, in order, lighter menstrual periods, fewer or weaker

menstrual cramps, decreases in mood, intermenstrual spotting, and vaginal discharge. The most common side effects reported by women taking antiandrogenic OCPs, in order, included lighter menstrual periods, fewer or weaker menstrual cramps, decreases in mood, decreases in acne, and bloating. It is of note that one-quarter of women taking androgenic OCPs reported increases in sexual desire, whereas one-third of women taking antiandrogenic OCPs reported decreases in sexual desire. The percentage of women endorsing vaginal dryness was also twice as high for women taking antiandrogenic OCPs compared to those taking androgenic OCPs (33.33% versus 16.00%, respectively). Refer to Table 13 for a list of possible side effects and frequency of endorsement by the two groups of women.

Table 13.

Frequency of Side Effects Endorsed by Women Taking Oral Contraceptive Pills

	Androgenic ***N*** **= 50**		**Antiandrogenic** ***N*** **= 21**	
Contraceptive side effect	***n***	**%**	***n***	**%**
Intermenstrual spotting	20	40.00	3	14.28
Lighter menstrual periods	38	76.00	14	66.66
Heavier menstrual periods	1	2.00	2	9.52
Missed periods	14	28.00	2	9.52
Fewer or weaker menstrual cramps	25	50.00	13	61.90
More or stronger menstrual cramps	6	12.00	1	4.76
Blood clots	3	6.00	1	4.76
Nausea	6	12.00	3	14.28

Table 13 (continued).

Bloating	15	30.00	9	42.85
Weight gain	11	22.00	4	19.04
Weight loss	1	2.00	0	0
Increased appetite	12	24.00	4	19.04
Decreased appetite	1	2.00	3	14.28
Decreases in mood	23	46.00	10	47.61
Improvements in mood	5	10.00	4	19.04
Headaches or migraines	6	12.00	6	28.57
Blurred vision	0	0	1	4.76
Increased acne	6	12.00	2	9.52
Decreased acne	15	30.00	10	47.61
Breast tenderness	10	20.00	7	33.33
Decreased libido	9	18.00	7	33.33
Increased libido	12	24.00	4	19.04
Vaginal discharge	16	32.00	5	23.80
Vaginal dryness	8	16.00	7	33.33
Other	1	2.00	1	4.76

Note: Women were instructed to endorse as many side effects as they experienced. Therefore, the total number reported is not equivalent to the total number of women in each of the two study groups. Only women taking oral contraceptive pills completed this measure. No significant between-group differences in contraceptive side effects emerged.

5.2.2. Group Variations in Sexual Distress

The average score on the Female Sexual Distress Scale-Revised for all groups was 8.26 (*SD* = 8.99), which is below the cutoff (11.00) for clinically meaningful distress (DeRogatis et al., 2008). This indicates that, on average, women who participated in this study did not experience clinical levels of sexual distress. Overall, the three groups of women reported similar levels of sexual distress: women taking androgenic OCPs reported the greatest level of sexual distress (*M* = 8.54, *SD* = 8.68), followed by women in the control group (*M* = 8.28, *SD* = 9.39), and then women in the antiandrogenic group (*M* = 7.52, *SD* = 8.99). An ANOVA found no between-group difference in sexual distress, $F(2) = 0.093$, $p = .911$.

5.2.3. Group Variations in Vulvovaginal Atrophy

Results from a chi-square test of independence indicated that women taking androgenic OCPs were significantly more likely to endorse vaginal bleeding associated with sexual activity than were women in the control group, $\chi^2(2, 130) = 9.759$, $p = .007$. Only one participant (1.69%) in the control group indicated they experience vaginal bleeding, whereas ten participants (20%) in the androgenic provided positive responses. A similar phenomenon was exhibited by women in the antiandrogenic group, with three participants (14.28%) endorsing vaginal bleeding associated with sexual activity. Analyses of the residuals, however, indicated that results from the antiandrogenic group were not significant, possibly due to the smaller group size ($n = 21$).

A MANOVA indicated no significant between-group differences for any of the remaining Vulvovaginal Atrophy Assessment items (i.e., dryness, itching/irritation,

dysuria, or pain), $F(2, 250) = 1.098$, $p = .365$, and an ANOVA confirmed there were no differences in the total score, $F(2) = 2.093$, $p = .127$. Given there was no association between group and dryness nor pain, the finding that vaginal bleeding was significantly elevated suggests that aspects of OCPs unrelated to vaginal dryness may also be at play. Refer to Table 14 for a summary of these results.

Table 14.

Item-Level Analysis of the Vulvovaginal Atrophy Assessment by Study Group

	Control ***N* = 59**		**Androgenic** ***N* = 50**		**Antiandrogenic** ***N* = 21**	
VVA item	***n***	**%**	***n***	**%**	***n***	**%**
Bleeding	1	1.69	10	20.00	3	14.28
	M	***SD***	***M***	***SD***	***M***	***SD***
Dryness	1.47	0.59	1.52	0.70	1.80	0.92
Itching/Irritation	1.37	0.61	1.62	0.69	1.52	0.67
Dysuria	1.13	0.39	1.18	0.43	1.14	0.35
Pain	1.40	0.59	1.62	0.75	1.52	0.60
Total score	5.38	1.56	5.94	1.59	6.00	1.58

Note: VVA = Vulvovaginal Atrophy Assessment; *M* = mean; *SD* = standard deviation. Bleeding was assessed using a binary Yes/No response. The numbers presented in this Table reflect positive (i.e., "yes") responses to the presence of vaginal bleeding associated with sexual activity. A significantly greater proportion of women in the androgenic group reported experiencing vaginal bleeding associated with sexual activity compared to women in either of the other two groups.

5.2.4. Group Variations in Positive Sexuality

The average score on the Positive Sexuality Survey for all study participants was 24.50 (*SD* = 4.56), which indicates that, on average, women who participated in this study had relatively positive views about their sexual activity. Overall, the three groups of women reported similar, positive views, with women in the control group reporting average scores of 24.84 (*SD* = 4.46). Similarly, women in the androgenic group reporting average scores of 24.70 (*SD* = 4.44), and women in the antiandrogenic group reporting average scores of 23.09 (*SD* = 5.05). An ANOVA found no significant between-group difference for this measure, $F(2) = 1.218$, $p = .299$. It appears as though, despite physiological hindrances of OCPs, women report feeling positive about their sexual experiences.

CHAPTER 6: DISCUSSION

6.1. GENERAL OVERVIEW

Genital sexual arousal in women, which principally consists of vaginal vasocongestion and lubrication, is critical to healthy sexual function and is intricately linked with hormone function. Estrogens play a key role in regulating women's genital arousal response (as reviewed in Santoro, Worsley, Miller, Parish, & Davis, 2016) and, as androgens are precursors in the biosynthesis of estrogens, androgens are also inherently integral to women's sexual function (as reviewed in Davis, Worsley, Miller, Parish, & Santoro, 2016). It is therefore likely that alterations in hormone levels may lead to alterations in sexual function.

Women may have sub- or supraphysiological levels of sex steroid hormones for a variety of reasons, including age (i.e., menopause), various medical conditions, and the use of hormonal contraceptives (Cohen & Goldstein, 2016). Oral contraceptive pills (OCPs), which are used by over a quarter of reproductive-age women in the United States (Daniels et al., 2015; Jones et al., 2013), contain either both ethinylestradiol and a synthetic progestin, or solely a synthetic progestin. Through progestin-induced hepatic increases in sex hormone binding globulin (SHBG), OCPs have been found to reduce the number of bioavailable androgens within women's bodies (Zimmerman et al., 2014). Oral contraceptive pills have also been associated with diminished self-reported sexual function (Hassanin et al., 2018; Pazandeh et al., 2017; Wallwiener et al., 2015; Zethraeus et al., 2016), increased vaginal dryness and vaginal pain (Smith et al., 2014), and decrements in objective measures of vaginal tissue integrity (Battaglia et al., 2012). This was the first

study to examine SHBG as a mediator of differences in vaginal blood flow and lubrication in women taking specific OCPs.

The primary aim of this dissertation was to examine differences in physiological vaginal blood flow and lubrication among women using OCPs containing low doses (i.e., ≤25 μg) of ethinylestradiol coupled with either an androgenic or antiandrogenic progestin. Serum concentrations of SHBG were also collected. Results from this study indicate there are physiological sexual side effects of OCPs based on pill androgenicity and related changes in SHBG concentrations. This dissertation also examined differences in self-reported and clinician-assessed sexual function among the groups of women, finding that the presence of physiologically based sexual arousal dysfunction was more prevalent in the group of women taking antiandrogenic OCPs compared to the other two study groups.

6.2. Summary of Results

It was hypothesized that physiological indices of sexual arousal would vary by hormonal state. Indeed, this was found to be the case. Women taking OCPs containing antiandrogenic progestins exhibited significantly lower levels of vaginal pulse amplitude (VPA) and lubrication compared to women taking androgenic OCPs or women in the control group. Responses on these measures for women taking OCPs containing androgenic progestins fell between women taking antiandrogenic OCPs and women in the control group, with the control group displaying the greatest physiological sexual arousal responses. Similarly, baseline (i.e., unaroused) levels of vaginal lubrication were significantly lower for women taking antiandrogenic OCPs than for women in the control group. Decrements in levels of post-film (i.e., aroused) lubrication were evidenced in

women taking both forms of OCPs; women in these two groups had significantly lower lubrication responses compared to women in the control group. These results indicate that OCPs containing ≤25 μg ethinylestradiol negatively impact women's physiological sexual arousal responses, and this is particularly true for OCPs containing antiandrogenic progestins. These findings bolster previous research suggesting that progestin components within hormonal contraceptives are highly influential in women's sexual functioning (e.g., Battaglia et al., 2012; Pazandeh et al., 2017; Zethraeus et al., 2016).

It was also hypothesized that the observed decrements in physiological sexual arousal would be mediated by changes in serum SHBG concentrations. Oral hormonal contraceptive pill use increases the hepatic production of SHBG and consequently decreases the amount of circulating, or free, androgens (as reviewed in Casey, MacLaughlin, & Faubion, 2016). Oral contraceptive pills also suppress androgen production from the ovaries (Burrows & Goldstein, 2013), thus having dual pathways leading to antiandrogenic effects. Despite significant relationships among study group, SHBG levels, and physiological sexual arousal, SHBG was not found to meaningfully mediate this relationship in the present study. That is, SHBG did significantly partially mediate several of the study's findings, though these effects were overshadowed by the strength of the preexisting relationships among the variables included in each model. Rather, a significant "chain reaction" appears to be at play, such that SHBG increased to varying extents based on women's hormonal profiles, which then led to significant between-group differences in physiological sexual arousal, but additional variables are needed to explain these relationships.

It is possible that a model containing both SHBG *and* androgen level as mediating variables may yield significant results. The increase in SHBG caused by the androgenicity of various progestins is not, directly, the cause of poor sexual function. Rather, bound androgens (i.e., androgens that have bound to SHBG) are rendered inactive and cannot interact with genital tissue and facilitate sexual arousal (for reviews relevant to OCP use, see Casado-Espada, de Alarcón, de la Iglesia-Larrad, Bote-Bonaechea, & Montejo, 2019; Palacios & Lilue, 2018). It is therefore plausible that a model containing androgen levels in addition to SHBG may be more likely to fully mediate the relationship between OCP use and physiological sexual arousal.

In opposition to these observed decrements in physiological sexual arousal, women taking OCPs displayed significantly *greater* subjective sexual arousal throughout the films. One possible explanation for this effect is that the sample of women taking OCPs may have been more sexually liberal and familiar with sexual films. As such, they may have been more mentally arousable to the sexual stimuli used in this study. Indeed, research has shown that, compared to naturally-cycling women, women taking OCPs report being more sexually experienced, holding less restrictive sexual morals, having greater interest in erotic material, and higher psychosexual motivation and enjoyment (Bancroft, Sherwin, Alexander, Davidson, & Walker, 1991).

Alternatively, it is possible that these observed effects were due to hormonal influences on women's attention to sexual stimuli. Eye-tracking studies indicate that both the content women attend to during exposure to sexual stimuli and the subjective ratings of attractiveness of this content vary based on OCP use. For example, naturally-cycling

women have been found to spend more time, and have a higher probability of, looking at genitals compared to women using OCPs, regardless of menstrual phase (Rupp & Wallen, 2007). Women taking OCPs, on the other hand, have been found to spend more time looking at, and have a higher probability of, looking at contextual aspects of sexual scenes (e.g., background images, clothing; Rupp & Wallen, 2007). Research has also shown that naturally-cycling women rate scenes that have a greater focus on the genitals as more arousing than do OCP users (Rupp & Wallen, 2009). It is, therefore, possible that films containing less content that directly focuses on the genitals may be less subjectively sexually arousing to naturally-cycling women. Retrospective review of the sexual stimuli used in the present study showed that, through my efforts to use sexual stimuli that would be considered "female-friendly" and sexually pleasing to an array of women, the majority of time within the sexual films did not focus explicitly on the genitals. On average, 554 seconds of the sexual film contained the actors' whole or mostly whole bodies, whereas there were, on average, only 46 seconds dedicated to close-up scenes of the genitals. As such, levels of subjective sexual arousal may have been influenced by the hormonal regulation of women's attention to the sexual stimuli.

We also hypothesized that differences in sexual function would be minimal and that the observed physiological decrements would not necessarily indicate the presence of sexual dysfunction. This hypothesis was largely supported. We found no between-group differences in self-reported sexual function as measured by the Female Sexual Function Index, suggesting that there were no overwhelming, global effects of OCP use on sexual function in this sample. Though this finding is consistent with the pattern of results found

in the present study (i.e., that physiological decrements occur in the absence of perceived sexual dysfunction), this finding contradicts past research that has found both increases (Çetin et al., 2015) and decreases (Wallwiener et al., 2015) in sexual function. It is possible that, given the relatively young age of the study participants, women in this dissertation had not been experiencing OCP-induced sexual arousal difficulties for a long enough period of time to experience a more global impact on their sexual function. For example, it may be that more chronic OCP-induced arousal difficulties might lead to repeated uncomfortable or unsatisfying sexual activity and/or feelings of concern surrounding lubrication, which may, in turn, lead to reduced desire to engage in sexual activity. This hypothesis aligns with Basson's (2000) circular model of sexual function, which suggests that engagement in positive sexual encounters may increase desire, whereas engagement in negative or unsatisfying sexual encounters may decrease desire for future sexual activity.

Whereas the literature is mixed with regards to self-reported non-physiological aspects of sexual function (e.g., desire; A. R. Davis & Castaño, 2004; Pastor, Holla, & Chmel, 2013; Roberts, Cobey, Klapilová, & Havlíček, 2013), a review of the literature indicated that decreases in lubrication, increases in vestibular pain, and thinning of the labia minora and vaginal introitus are common among combined OCP users (Burrows et al., 2012). In line with this extant literature, measures within the present study that more directly assessed physiological aspects of sexual arousal, particularly vaginal bleeding and lubrication (i.e., the Vulvovaginal Atrophy Assessment and clinical interview), yielded significant effects of OCPs on physiological sexual function. This continues to suggest that the sexual side effects of OCPs may primarily be organic in nature.

The high rates of vaginal bleeding after sexual activity found in the present study are likely due to the thinning of the vaginal tissue and/or cervical alterations. There is a high density of androgen receptors within the vaginal tissue, indicating that testosterone is essential for the maintenance of healthy tissue (I. Goldstein, 2009). As such, reductions in androgen levels (as observed in women taking OCPs; Zimmerman et al., 2014) may negatively impact the vaginal epithelium. Furthermore, vaginal tissue is also responsive to estrogen. It is possible that OCP use may lead to vaginal tissue atrophy through differences in responsiveness to naturally-occurring estrogen (i.e., 17β-estradiol) and synthetic ethinylestradiol (for a synthesis of the research examining hormones and genital tissue, see I. Goldstein, 2009). In other words, vaginal tissue may be more responsive to 17β-estradiol and less responsive to synthetic ethinylestradiol, thus leading to thinner vaginal tissue. Thinner tissue is more likely to lead to vaginal tearing and thus bleeding (Kagan & Rivera, 2018) and is a possible explanation for the increased rates of bleeding associated with sexual activity seen in the present study.

Women taking OCPs are also more likely to experience cervical ectopy and inflammation (Bright et al., 2011; Ocak et al., 2007). Cervical ectopy, which refers to when cells from within the cervical canal are present on the outside surface of the cervix, and cervical inflammation have both been linked with vaginal bleeding after sexual intercourse (Patil & Sharma, 2017). In a 12-month longitudinal study examining, in part, the effects of hormonal contraceptives on genital tissue, Bright and associates (2011) found large areas of cervical ectopy in 17.4% of women taking OCPs. These findings are supported by previous cross-sectional (Critchlow et al., 1995; Goldacre et al., 1978; Mali, Hunter,

Maggwa, & Tukei, 1995) and longitudinal (Louv, Austin, Perlman, & Alexander, 1989; Rahm, Gnarpe, & Odlind, 1988) research, and aligns well with the prevalence of vaginal bleeding in the current study (17.14% for the androgenic and antiandrogenic groups, combined). It is, therefore, possible that cervical ectopy contributed to the observed rates of vaginal bleeding.

It is worth noting that the effects observed in the present study are likely conservative. In an attempt to approximate the hormonal profiles of women taking OCPs, all study sessions for naturally-cycling women were conducted within the luteal phase of the menstrual cycle. However, as sexual function is closely linked to hormone expression (S. R. Davis et al., 2016; Worsley, Santoro, Miller, Parish, & Davis, 2016), aspects of women's sexual function vary across the menstrual cycle. For example, rates of sexual fantasy and desire are higher during the follicular compared to luteal phase (S. G. Brown et al., 2011; Dawson et al., 2012), as well as sexual arousal, engagement in sexual activity, and rates of orgasm (S. G. Brown et al., 2011; Caruso et al., 2014; Clayton et al., 1999; Graham et al., 2000). By this nature, it is likely that greater differences in sexual arousal and function would have been observed had study sessions for naturally-cycling women been conducted within the follicular phase.

6.3. IMPLICATIONS

This dissertation has several important clinical and methodological implications. First, the present research helps clarify variations in both physiological and self-reported (i.e., subjective sexual arousal and perceived genital arousal) sexual arousal among women taking OCPs with differing hormonal profiles. Second, as all OCPs included in this study

contained low doses of ethinylestradiol, we were able to parse apart the specific effects of the androgenic properties on women's sexual arousal responses. Not only does this research enhance our understanding of the effects of OCPs on vaginal blood flow, a commonly examined marker of genital sexual arousal, but it also elucidates the effects of OCPs on physiological vaginal lubrication, a marker typically examined via self-report. Third, examining the mechanistic role of SHBG in these relationships helps to explain *how* such effects occur, as well as enhances our understanding of the important role testosterone plays in women's physiological sexual arousal responses. To my knowledge, this was the first study to examine variations in physiological measures of vaginal lubrication among women taking OCPs.

6.3.1. Clinical Implications

Decrements in both vaginal blood flow and lubrication were observed in women in both OCP groups, providing empirical support for negative physiological sexual side effects of these medications. This finding has implications for OCP prescription and management; women at risk for sexual arousal dysfunction (e.g., diagnosed with diabetes, heart disease; McCabe et al., 2016) should be prescribed OCPs, particularly antiandrogenic OCPs, with caution and thorough consultation of relevant sexual side effects. For women taking OCPs who present with sexual arousal dysfunction, clinicians should assess the androgenicity of the pill and make changes to alter the woman's hormonal profile to allow for a greater amount of free testosterone.

One manner in which clinicians may choose to alter women's levels of free testosterone is through dehydroepiandrosterone supplement. Indeed, one study examining

the effect of a drospirenone-containing OCP (i.e., an antiandrogenic OCP) co-administered with dehydroepiandrosterone suggested such a combination may improve OCP-related reductions in sexual function (Zimmerman et al., 2015). In this study, 99 women were randomized to receive daily doses of 3 mg drospirenone coupled with 30 μg ethinylestradiol in conjunction with either 50 mg dehydroepiandrosterone or placebo. Though no significant effects were found for the dehydroepiandrosterone group, trends towards improved sexual function were noted. The authors concluded that, whereas 50 mg dehydroepiandrosterone restored total testosterone to pre-OCP levels, free testosterone was only restored by 47%. It may be necessary to restore completely women's levels of free testosterone to see significant and clinically meaningful improvements in sexual function. It is important to note, however, that this study did not examine physiological changes in the genital tract or sexual function. It is therefore unknown whether any improvements in sexual function through dehydroepiandrosterone supplementation would translate from those seen in women's self-reports to organic and/or physiological improvements. A case study has, however, reported improvements to the vulvar vestibule in a woman with OCP-induced vaginal pain after OCP cessation and local administration of testosterone and estradiol (A. T. Goldstein, Burrows, & Goldstein, 2010).

Alternatively, clinicians may suggest an OCP containing estradiol valerate, a synthetic, though considered natural and bioidentical, form of estrogen. The estradiol valerate plus dienogest OCP has been found to have good contraceptive efficacy (Endrikat et al., 2008; Palacios et al., 2010) and cycle control (Ahrendt, Makalová, Parke, Mellinger, & Mansour, 2009). Natural estradiol is a less stable compound than synthetic

ethinylestradiol and, therefore, increases SHBG concentrations to a lesser extent (Millán & Castañeda, 2014). Indeed, several studies have examined estradiol valerate-induced hepatic protein synthesis and have consistently found less pronounced changes in SHBG and other hepatic-related syntheses compared to that of ethinylestradiol (Junge, Mellinger, Parke, & Serrani, 2011; Klipping et al., 2011; Lindberg, Crona, Stigendal, Teger-Nilsson, & Silfverstolpe, 1989; Wiegratz, Lee, Kutschera, Winkler, & Kuhl, 2004). It is, therefore, possible that an estradiol valerate-containing OCP may impact sexual arousal and overall function to a lesser extent than ethinylestradiol-containing OCPs. Several studies have, in fact, found enhancing effects of the estradiol valerate plus dienogest OCP on sexual function (Caruso et al., 2016; Di Carlo et al., 2014; Osmanağaoğlu, Atasaral, Baltaci, & Bozkaya, 2006), with one study finding no difference between this OCP and an androgenic OCP containing ethinylestradiol plus levonorgestrel (S. R. Davis et al., 2013). For patients who struggle with OCP-induced sexual dysfunction who wish to remain on an OCP, transitioning to an estradiol valerate-containing OCP may be advisable.

Finally, the finding that women taking OCPs frequently endorsed vaginal bleeding with sexual activity is also clinically relevant. It is unknown whether this may be due to tearing of the vaginal tissue, cervical alterations, or through additional OCP-induced changes. Both vaginal tearing and cervical ectopy increase the likelihood of contracting sexually transmitted infections (e.g., Fethers, Fairley, Hocking, Gurrin, & Bradshaw, 2008; Srinivasan et al., 2012). In fact, a recent systematic review found cervical ectopy to be positively associated with numerous sexually transmitted infections, such as human papillomavirus, human immunodeficiency virus, and bacterial vaginosis (Soares, Braz,

Araújo, & Oliveira, 2019). This is problematic as women taking OCPs are less likely to also use barrier methods than those who are not. Cross-cultural research has demonstrated that only about 12-23% of women using hormonal contraceptives also use condoms during sexual activity (Centers for Disease Control and Prevention, 2012; Chibwesha et al., 2011; Eisenberg, Allsworth, Zhao, & Peipert, 2012; Harvey, Henderson, & Branch, 2004) and are therefore at greater risk for contracting an infection. Women taking OCPs should be counseled on this increased risk and encouraged to use barrier methods in addition to their OCP to reduce the likelihood of contracting an infection.

6.3.2. Methodological Implications

Results from this study also have methodological implications for sexual psychophysiological researchers. Based on these results, researchers within this area are urged to carefully consider the inclusion of women taking OCPs (especially when heterogeneously included), as the stark differences in physiological responding could mask true effects within the data and lead to inaccurate conclusions. Few sexual psychophysiological studies currently control for hormonal contraceptive use despite reporting that these were used by members of the sample (e.g., Bird, Seehuus, Clifton, & Rellini, 2014; Both et al., 2015; Velten, Scholten, Graham, Adolph, & Margraf, 2016). Furthermore, several studies fail to report whether participants were taking hormonal contraceptives altogether (e.g., Huberman, Suschinsky, Lalumière, & Chivers, 2013; Klein, Hill, Chang, Hillard, & Gorzalka, 2012; Vilarinho et al., 2014). When researchers do examine potential differences in women who are and are not taking OCPs, the composition of the OCP is not always considered (e.g., Brom et al., 2016; Suschinsky &

Lalumière, 2012). Results from the present research indicate that it is critical OCP use be taken into consideration when designing and recruiting for studies of this nature. There are striking differences in VPA between women taking androgenic and antiandrogenic OCPs. Failing to screen for this information and/or analyze separately could hinder research outcomes by masking true effects.

6.4. LIMITATIONS

This study has a few limitations that warrant mention. First, the majority of women who participated were heterosexual (74.61%) and college-aged (M = 20.12 years, SD = 2.53). Though these demographic groups are the most likely to use OCPs and thus this study maps on nicely to these particular populations (Daniels et al., 2015; Jones et al., 2013), many non-heterosexual and non-college-aged women do use OCPs. The application of the results of this study to less-represented populations is limited.

Another limitation of this research is that the lubrication test strip was self-administered. Although caution was taken when instructing participants where and how to insert the test strip to minimize between-person variability, it is possible that not all participants inserted the test strip correctly. This could have interfered with the accuracy of these particular data and potentially impacted the study results. Ideal circumstances would have been for a researcher to administer the measure to the participant, but this was not feasible to do within the setting in which the study took place. Relatedly, though extreme efforts were taken to match the four erotic films for content, some women likely found certain films more arousing than others. It is possible, though unlikely, that

preferences for certain settings or certain actors contributed to the observed differences in genital or subjective arousal.

Finally, women in the control group likely had varying hormonal profiles, some of which may have looked similar to those of women in either of the two OCP groups. Though all study sessions for naturally-cycling women were conducted during the luteal phase of their menstrual cycle to minimize such hormonal differences, each woman likely had different estrogen, progesterone, and androgen levels, which could have interfered with the collected data. Indeed, research employing commercial immunoassays suggests that concentrations of serum estradiol ranges between 20 and 80 picograms per milliliter (pg/mL) during the follicular phase of the menstrual cycle, peaks at a range of 200 to 500 pg/mL during preovulation, and plummets after ovulation occurs (Hobeika et al., 2020). Serum progesterone, contrastingly, is low during the follicular phase, with average levels of less than 1.5 nanograms per milliliter (ng/mL). Levels peak around ovulation and are usually greater than 7 ng/mL during the luteal phase, with some experts suggesting that levels as high as 15 ng/mL are indicative of normal luteal function. Testosterone levels are more consistent, with typical ranges between 20 and 50 nanograms per deciliter (Hobeika et al., 2020). Such ranges have implications for varying SHBG concentrations and, according to the results of the present study, physiological sexual arousal. Future research should more closely examine sexual function as it relates to naturally occurring variations in hormone levels.

6.5. Future Directions

The results of this research indicate that OCPs influence the physiological responding of genital tissue. However, as this study was not prospective or randomized in design, it is possible that participants self-selected into their study groups. That is to say, many women (19; 26.76%) in the two OCP groups reported past use of a different OCP, with some women citing side effects (both sexual and nonsexual in nature) as their reasons for these changes. Alternatively, some women selected their OCP based on the side-effect profile. For example, OCPs containing antiandrogenic progestins are often prescribed to women wishing to alleviate concerns such as acne and/or oily skin (e.g., Lortscher, Admani, Satur, & Eichenfield, 2016). Though the possibility for self-selection does not cast a great deal of doubt onto the results of the present study, future research should employ prospective, randomized clinical trials to minimize the potential for such bias.

In addition to prospective, randomized clinical trials, our understanding of the effects of OCPs on women's bodies would be greatly enhanced through the use of long-term follow-up and discontinuation studies. There is research to suggest that the physiological effects of OCPs may not be entirely reversible or may endure for an unknown period of time after discontinuation. In a cross-sectional study, Panzer and colleagues (2006) examined SHBG concentrations in 124 premenopausal women who were at different stages of OCP use: no history of OCP use, current OCP use, and past OCP use. Consistent with the present study, SHBG concentrations in the current OCP users were, on average, four times higher than those of women who have never used OCPs. A decrease in SHBG was noted in the group of women who had discontinued OCP use, though they

remained significantly elevated compared to women with no history of OCP use. This effect was found at a minimum of 120 days post-discontinuation. A separate study examining SHBG and androgen levels in eight women with polycystic ovarian syndrome found SHBG, testosterone, and dehydroepiandrosterone sulfate had returned to pre-OCP levels 8 weeks after discontinuation (Sánchez et al., 2007). It is important to note, however, that women in these two studies used OCPs for drastically different amounts of time: OCP users and discontinuers in the Panzer et al. study were required to have used OCPs for at least 6 months, whereas women in Sánchez et al. took OCPs for 3 months. It is, therefore, possible that it takes longer for androgen and SHBG concentrations to return to pre-OCP levels with longer OCP use. This speculation warrants research attention; many women in the present study reported many years (maximum of 5 years) of continuous OCP use.

Sex hormone binding globulin was not found to mediate the relationship between OCP use and physiological sexual arousal, though it was very strongly associated with each of these variables. Future research should examine downstream hormonal changes as potential mediators of this relationship. It is possible that androgen levels may be a more suitable candidate mediator, as the hypothesized mechanism of action for SHBG on physiological sexual arousal is through decreased androgen levels.

It would also be worth examining the degree to which physiological sexual arousal varies in women using OCPs with high doses (i.e., ≥30 μg) of ethinylestradiol compared to women taking OCPs with low doses (i.e., ≤25 μg) of ethinylestradiol or those who are naturally-cycling. It is likely that high doses of ethinylestradiol would negatively influence physiological sexual arousal for a number of reasons. Research examining the effects of

exogenously administered estradiol on vaginal tissue growth and structure found that subphysiological (5 μg) doses of estradiol were superior (i.e., facilitated greater tissue growth) to supraphysiological (45 μg) doses (Pessina et al., 2006). In this study, rats were ovariectomized and provided with continuous estradiol infusions of varying concentrations for two weeks. Greater tissue growth was observed in both the vaginal epithelium and muscularis (i.e., the outer and middle layers of the vaginal wall) in rats that had received the *subphysiological* doses of estradiol. Thick vaginal tissue is beneficial as it is less susceptible to abrasion, infection, and disturbances in sensation (Mac Bride et al., 2010). Furthermore, thick vaginal tissue is thought to allow for greater blood flow due to increases in the number and density of blood vessels and capillary beds (Mac Bride et al., 2010).

Estrogen also stimulates SHBG production, and greater amounts of SHBG leads to fewer bioavailable androgens. As such, greater levels of estrogen should lead to a greater increase in SHBG, which would, in turn, lead to lesser amounts of bioavailable androgens and, in line with the results of the present study, poorer physiological sexual arousal. Indeed, research has found that OCPs containing low doses of ethinylestradiol are linked with lower levels of SHBG than are OCPs containing high doses of ethinylestradiol (Zimmerman et al., 2014). Therefore, future research should examine the extent to which physiological sexual arousal is impacted in women taking OCPs containing high doses of ethinylestradiol.

6.6. CONCLUSION

To my knowledge, this was the first study to compare multiple measures of physiological sexual arousal across groups of women taking OCPs with varying hormonal

profiles. The current study helps elucidate the relationship between progestin androgenicity and genital arousal function; antiandrogenic progestins had deleterious effects on vaginal blood flow and lubrication Compared to naturally-cycling women, women taking androgenic progestins also exhibited dampened physiological responses. Self-reported vaginal dryness and bleeding, as well as clinical assessments of female sexual arousal disorder, were also notably elevated in women taking OCPs. Furthermore, as the naturally-cycling women were assessed during the luteal phase of their menstrual cycle, the between-group differences observed in the present study are likely conservative; greater differences are likely to occur mid-cycle. These findings expand our understanding of the effect of hormones on genital tissue function and the physiological sexual side effects of OCPs and suggest avenues for future investigation of the sexual arousal responses in women taking OCPs.

APPENDICES

APPENDIX A: CONTRACEPTIVE HISTORY

Form of contraceptive: □ Pill □ Other

Name of Pill: _____

Dose of ethinylestradiol: _____

Progestin name and dose: _____

When did you begin using this OCP: _____

Have you used other forms of hormonal contraceptives?

□ Yes □ No

If yes, list names and years used: _____

_____

If yes, why did you switch? *(probe for any side effects)*: _____

_____

APPENDIX B: FEMALE SEXUAL DYSFUNCTION DIAGNOSIS

Have you ever experienced…	**What are you experiencing now?**	**How important is it for you to feel this during sexual activity?**
pleasurable sexual feelings in your genitals from stimulation of your genital area? □ Yes □ No	□ Same as in the past □ Lower intensity □ No longer experiencing this	1 = Not important 2 = Moderately unimportant 3 = About equally important/unimportant 4 = Moderately important 5 = Very important
genital pulsing or throbbing? □ Yes □ No	□ Same as in the past □ Lower intensity □ No longer experiencing this	1 = Not important 2 = Moderately unimportant 3 = About equally important/unimportant 4 = Moderately important 5 = Very important
genital or clitoral fullness, pressure or engorgement? □ Yes □ No	□ Same as in the past □ Lower intensity □ No longer experiencing this	1 = Not important 2 = Moderately unimportant 3 = About equally important/unimportant 4 = Moderately important 5 = Very important
genital warmth? □ Yes □ No	□ Same as in the past □ Lower intensity □ No longer experiencing this	1 = Not important 2 = Moderately unimportant 3 = About equally important/unimportant 4 = Moderately important 5 = Very important
genital wetness or lubrication? □ Yes □ No	□ Same as in the past □ Lower intensity □ No longer experiencing this	1 = Not important 2 = Moderately unimportant 3 = About equally important/unimportant 4 = Moderately important 5 = Very important

Question	**Response**
Based on your responses to these questions, do you think you have an arousal problem now (difficulty getting or staying aroused)?	□ Yes □ No

If yes…

1. Do your arousal difficulties occur in:	□ All types of situations (e.g., during partnered sexual activity AND masturbation)

	□ Certain types of situations
2. Was there ever a time when you were able to get and stay sexually aroused?	□ Yes □ No
3. For how long have you been experiencing these arousal difficulties?	_____years _____months
4. Is this distressing to you?	□ Yes □ No
5. If so, why is distressing to you?	□ Because it makes my partner unhappy, frustrated, or distressed □ Because it makes me unhappy, frustrated, or distressed □ Both

For OCP groups:
If she reports <u>any</u> difficulties with sexual arousal, ask:

1. Did these difficulties begin before or after you began using the form of oral contraceptive that you are currently taking?
   □ Yes □ No
2. Do you believe these difficulties are related to your OCP in any way?

□ Yes □ No
If yes, please explain: _____
_____

APPENDIX C: FILM SCALE

Pre-Film Scale

Please use the following scale to evaluate how you currently feel. Please answer honestly and carefully. On the scale, circle the number which best describes how you currently feel from 1 (not at all) to 7 (intensely).

Currently, I feel:

	Not at all						Intensely
1. Warmth in genitals_____	1	2	3	4	5	6	7
2. Genital wetness or lubrication__	1	2	3	4	5	6	7
3. Genital pulsing or throbbing____	1	2	3	4	5	6	7
4. Genital tenseness or tightness___	1	2	3	4	5	6	7
5. Any genital feeling_____	1	2	3	4	5	6	7
6. ***IF*** you are currently experiencing any of the above sensations, to what extent are they:	1	2	3	4	5	6	7
……***pleasant*** for you?							
……....***negative*** for you?	1	2	3	4	5	6	7
……***uncomfortable*** for you?	1	2	3	4	5	6	7
…….. ***positive*** for you?	1	2	3	4	5	6	7
……..***distressing*** for you?	1	2	3	4	5	6	7
……***appealing*** for you?	1	2	3	4	5	6	7
…… ***sexual*** for you?	1	2	3	4	5	6	7

Currently, I feel:

	Not at all						Intensely
7. Sexually aroused_____	1	2	3	4	5	6	7
8. Mental sexual arousal_____	1	2	3	4	5	6	7
9. Sexually turned off_____	1	2	3	4	5	6	7

Post-Film Scale

Please use the following scale to evaluate how you felt during your film session. Please answer honestly and carefully. On the scale, circle the number which best describes how you felt during the film from 1 (not at all) to 7 (intensely).

During the film, I felt:

	Not at all						Intensely
1. Warmth in genitals_____	1	2	3	4	5	6	7
2. Genital wetness or lubrication__	1	2	3	4	5	6	7
3. Genital pulsing or throbbing____	1	2	3	4	5	6	7
4. Genital tenseness or tightness___	1	2	3	4	5	6	7
5. Any genital feeling_____	1	2	3	4	5	6	7
6. ***IF*** you experienced any of the above sensations, to what extent were they:							
……***pleasant*** for you?	1	2	3	4	5	6	7
…….....***negative*** for you?	1	2	3	4	5	6	7
……***uncomfortable*** for you?	1	2	3	4	5	6	7
…….. ***positive*** for you?	1	2	3	4	5	6	7

……..***distressing*** for you?	1	2	3	4	5	6	7
……***appealing*** for you?	1	2	3	4	5	6	7
…… ***sexual*** for you?	1	2	3	4	5	6	7

During the film, I felt:

	Not at all						Intensely
7. Sexually aroused_____	1	2	3	4	5	6	7
8. Mental sexual arousal_____	1	2	3	4	5	6	7
9. Sexually turned off_____	1	2	3	4	5	6	7

APPENDIX D: DEMOGRAPHICS

1. What is your date of birth? (month/day/year) _____

2. What is your age? _____ years

3. What is your menopausal status?
   __Premenopausal
   __Perimenopausal (i.e., transitioning from pre- to postmenopausal)
   __Postmenopausal
   __Unsure

4. Are you currently taking an oral contraceptive pill?
Yes No
   a. If yes, please write out the exact name of your oral contraceptive as it appears on your prescription, including any information on dose:
   b. If no, please list the form of contraception you use (e.g., condoms), if any:

5. Are you currently taking any **other** prescription medications?
Yes No
   a. If yes, please list them below:

6. Are you currently taking any **non-prescription** medications (e.g., vitamins)?
Yes No
   a. If yes, please list them below:

7. Please indicate you highest level of education:
   __Some high school or less
   __High school graduate/GED
   __Some college
   __4 years college
   __Advanced degree (Ph.D., M.S., J.D., etc.)

8. What is your yearly household income?
   __Less than $50,000
   __$50,001 to $100,000
   __More than $100,000

9. Please indicate your ethnicity: Hispanic/Latina Not Hispanic/Latina

10. The country of your heritage: _____

11. Please indicate your race (check all that apply):

__Native American
__African American/Black
__Caucasian/White
__Hispanic/Latin American
__Asian
__Pacific Islander/Hawaiian Native
__Middle Eastern
__Other; please specify

12. What, if any, are your religious beliefs? You may only select one, so please choose which you most identify with.
__Not religious
__Atheist / Agnostic
__Spiritual / New Age
__Christianity
__Catholicism
__Judaism
__Islam
__Hinduism
__Buddhism
__First Nations / Native American Beliefs
__Taoism
__Jainism
__Wicca
__Other:

13. Please indicate your relationship status:
__Single, not dating
__Single, dating
__In a committed relationship (with one partner)
__In a committed relationship (with multiple partners)
__Living with a partner
__Married
__Other, please specify

14. If you are in a relationship, please indicate the duration of your current relationship: _____

15. What sexual orientation do you identify with?
___ Heterosexual, Straight
___ Bisexual
___ Pansexual
___ Queer
___ Homosexual, Gay, Lesbian

___ Asexual
___ I prefer not to identify my sexual orientation with a label.
___ Other, please specify

16. How old were you when you first had consensual sex with a partner (e.g., vaginal intercourse or however you define sex)? _____ years

17. Have you ever experienced unwanted or non-consensual sexual activity (e.g., oral sex, vaginal intercourse, genital fondling)?

Yes No

    a. If yes, at what age(s) did this occur?

18. How often do you use lubricants (e.g., KY Jelly) for vaginal intercourse?
    a. 5 = Almost always or always
    b. 4 = Most times (more than half the time)
    c. 3 = Sometimes (about half the time)
    d. 2 = A few times (less than half the time)
    e. 1 = Almost never or never

19. For you, how acceptable is it to use lubricants (e.g., KY Jelly) for vaginal intercourse?
    a. 5 = Completely acceptable
    b. 4 = More acceptable than unacceptable
    c. 3 = Neutral
    d. 2 = More unacceptable then acceptable
    e. 1 = Not at all acceptable

APPENDIX E: CONTRACEPTIVE SIDE EFFECTS

Below is a list of possible side effects of various oral contraceptive pills. Please endorse as many of the side effects that you have experienced over the past **3 months**.

If you can **clearly** attribute any of the below side effects to reasons other than your oral contraceptive pill (e.g., weight loss due to dieting, decreases in acne due to a new skin care routine), please do **not** endorse them.

1. Intermenstrual spotting
2. Lighter menstrual periods
3. Heavier menstrual periods
4. Missed periods
5. Fewer or weaker menstrual cramps
6. More or stronger menstrual cramps
7. Blood clots
8. Nausea
9. Bloating
10. Weight gain
11. Weight loss
12. Increased appetite
13. Decreased appetite
14. Decreases in mood (e.g., sadness)
15. Improvements in mood
16. Headaches or migraines
17. Blurred vision
18. Increased acne
19. Decreased acne
20. Breast tenderness
21. Decreased libido/sexual desire/interest
22. Increased libido/sexual desire/interest
23. Vaginal discharge
24. Vaginal dryness
25. Other (please specify)

APPENDIX F: FEMALE SEXUAL FUNCTION INDEX

These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. In answering these questions the following definitions apply:

Sexual activity includes intercourse, caressing, foreplay, masturbation, deep kissing and petting.

Sexual intercourse is defined as penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CIRCLE ONLY ONE CHOICE PER QUESTION:

Sexual desire or interest is a feeling that included wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how often did you feel sexual desire or interest?
   5 = Almost always or always
   4 = Most times (more than half the time)
   3 = Sometimes (about half the time)
   2 = A few times (less than half the time)
   1 = Almost never or never

2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?
   5 = Very high
   4 = High
   3 = Moderate
   2 = Low
   1 = Very low or none at all

3. Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?
   5 = Almost always or always
   4 = Most times (more than half the time)
   3 = Sometimes (about half the time)
   2 = A few times (less than half the time)
   1 = Almost never or never

4. Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?
   5 = Very high
   4 = High
   3 = Moderate
   2 = Low
   1 = Very low or none at all

5. Over the past 4 weeks, how confident were you about becoming sexually aroused during sexual activity or intercourse?	5 = Very high confidence 4 = High confidence 3 = Moderate confidence 2 = Low confidence 1 = Very low or no confidence
6. Over the past 4 weeks, how often have you been satisfied with your arousal (excitement) during sexual activity or intercourse?	5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
7. Over the past 4 weeks, how often did you become sexually aroused (lubricated or "wet") during sexual activity or intercourse?	5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
8. Over the past 4 weeks, how difficult was it to become aroused (lubricated or “wet") during sexual activity or intercourse?	1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
9. Over the past 4 weeks, how often did you maintain your arousal (lubrication or "wetness") until completion of sexual activity or intercourse?	5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
10. Over the past 4 weeks, how difficult was it to maintain your arousal (lubrication or "wetness") until completion of sexual activity or intercourse?	1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?	5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?	1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
13. Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?	5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied and dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
14. Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?	5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied and dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
15. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?	5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied and dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
16. Over the past 4 weeks, how satisfied have you been with your overall sexual life?	5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied and dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
17. Over the past 4 weeks, how often did you experience discomfort or pain during vaginal penetration?	1 = Almost always or always 2 = Most times (more than half the time) 3 = Sometimes (about half the time) 4 = A few times (less than half the time) 5 = Almost never or never N/A = No vaginal penetration

18. Over the past 4 weeks, how often did you experience discomfort or pain following vaginal penetration?

1 = Almost always or always
2 = Most times (more than half the time)
3 = Sometimes (about half the time)
4 = A few times (less than half the time)
5 = Almost never or never
N/A = No vaginal penetration

19. Over the past 4 weeks, how would you rate your level (degree) of discomfort or pain during or following vaginal penetration?

N/A = No sexual activity 1 = Very high
2 = High
3 = Moderate
4 = Low
5 = Very low or none at all
N/A = No vaginal penetration

APPENDIX G: FEMALE SEXUAL DISTRESS SCALE - REVISED

In the last week, how often did you feel…

	Never	Rarely	Occasionally	Frequently	Always
1. Distressed about your sex life	0	1	2	3	4
2. Unhappy about your sexual relationship	0	1	2	3	4
3. Guilty about sexual difficulties	0	1	2	3	4
4. Frustrated by your sexual problems	0	1	2	3	4
5. Stressed about sex	0	1	2	3	4
6. Inferior because of sexual problems	0	1	2	3	4
7. Worried about sex	0	1	2	3	4
8. Sexually inadequate	0	1	2	3	4
9. Regrets about your sexuality	0	1	2	3	4
10. Embarrassed about sexual problems	0	1	2	3	4
11. Dissatisfied with your sex life	0	1	2	3	4
12. Angry about your sex life	0	1	2	3	4
13. Bothered by low sexual desire	0	1	2	3	4

APPENDIX H: VULVOVAGINAL ATROPHY ASSESSMENT

To what extent do you experience each of the following…

	None	Mild	Moderate	Severe
1. Vaginal dryness	0	1	2	3
2. Vaginal and/or vulvar irritation/itching	0	1	2	3
3. Dysuria (painful or difficult urination)	0	1	2	3
4. Vaginal pain associated with sexual activity	0	1	2	3

Do you experience…

1. Vaginal bleeding associated with sexual activity	Yes	No

APPENDIX I: POSITIVE SEXUALITY SURVEY

Over the past four weeks…

	Strongly agree	Agree	Somewhat agree	Somewhat disagree	Disagree	Strongly disagree
I have felt confident in my ability to become lubricated/"wet" during sexual arousal.	1	2	3	4	5	6
I have felt satisfied with my ability to become lubricated/"wet" during sexual arousal.	1	2	3	4	5	6
After engaging in sexual activity, I have felt positively about (or pleased with) my ability to perform sexually.	1	2	3	4	5	6
I have felt positively about (or pleased with) my overall sexual life.	1	2	3	4	5	6
My sexual experiences have felt rewarding.	1	2	3	4	5	6

GLOSSARY OF TERMS

Androgenic: The extent to which sex hormone binding globulin is upregulated, leading to an increase in this protein and a decrease in androgen levels. In the present context, a relative androgenicity of >.5mg

Androgenicity: The extent to which physiological reactions similar to those produced by androgens are present. In the present context, the extent to which sex hormone binding globulin is upregulated

Antiandrogenic: The extent to which sex hormone binding globulin is upregulated, leading to an increase in this protein and a decrease in androgen levels. In the present context, a relative androgenicity of ≤.5mg

Ethinylestradiol: A synthetic derivative of the natural estrogen 17β-estradiol. It is found in nearly all combined forms of oral contraceptive pills

Female sexual arousal disorder: Defined by *DSM-IV-TR* as a persistent or recurrent inability to attain or maintain an adequate lubrication-swelling response until completion of sexual activity, must cause persistent or marked distress or interpersonal difficulty

Sex hormone binding globulin: A protein produced by the liver. It binds tightly to the sex steroid hormones estrogen, dihydrotestosterone, and testosterone, rendering them inactive

Subjective sexual arousal: The cognitive or emotional experience of sexual arousal; feeling "turned on" in one's mind

Vaginal pulse amplitude: A psychophysiological index that reflects short-term changes in the engorgement of blood in the vaginal tissue; an index of women's physiological, or genital, arousal

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